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<p>(54) Title: MULTIPLE TARGET HYBRIDIZING NUCLEIC ACIDS, THEIR PREPARATION, COMPOSITIONS, FORMULATION, KITS AND APPLICATIONS</p> <p>(57) Abstract</p> <p>Antisense oligonucleotides which bind to two or more RNA targets are disclosed.</p>		

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## MULTIPLE TARGET HYBRIDIZING NUCLEIC ACIDS, THEIR PREPARATION, COMPOSITIONS, FORMULATION, KITS & APPLICATIONS

### BACKGROUND OF THE INVENTION

#### Field of the Invention

5           This invention relates to multiple target anti-sense oligonucleotides (MTA oligos) of low or no adenosine content. The present agents are effective in the prophylaxis and treatment of diseases and conditions associated with inflammation, impaired airways, including lung disease and diseases whose secondary effects afflict the lungs of a subject. The agents are targeted to specific genes, genomic flanking regions, initiation codon, intron-exon borders, and  
10           the like, or the coding and non-coding regions of RNAs, including those encoding certain proteins, particularly those associated with diseases having multiple mediators, by affecting (either attenuating or enhancing) various contributing pathways. Examples are pulmonary diseases such as allergies, asthma, impeded respiration, pain, cystic fibrosis and cancers such as leukemias, e.g. colon cancer, and the like. The present agent may easily be administered  
15           prophylactically and therapeutically in conjunction with other therapies, or may be utilized as a substitute for therapies that have significant, negative side effects.

#### Description of the Background

          Respiratory ailments, associated with a variety of diseases and conditions, are extremely common in the general population, and more so in certain ethnic groups, such as African  
20           Americans. In some cases they are accompanied by inflammation, which aggravates the condition of the lungs. Asthma, for example, is one of the most common diseases in industrialized countries. In the United States it accounts for about 1% of all health care costs. An alarming increase in both the prevalence and mortality of asthma over the past decade has been reported, and asthma is predicted to be the preeminent occupational lung disease in the  
25           next decade. While the increasing mortality of asthma in industrialized countries could be attributable to the increased reliance upon beta agonists in the treatment of this disease, the underlying causes of asthma remain poorly understood.

          Anti-sense oligonucleotides have received considerable theoretical consideration as potential useful pharmacological agents in human disease. Their practical application in actual  
30           models of human disease, however, has been somewhat elusive. One important impediment to their effective application has been a difficulty in finding an appropriate route of administration to deliver them to their site of action. Many in vivo experiments were conducted by administering anti-sense oligonucleotides directly to specific regions of the brain. These applications, however, necessarily have limited clinical utility due to their invasive nature.

35           The systemic administration of anti-sense oligonucleotides also presents significant problems, not the least being an inherent difficulty in targeting disease-involved tissues. In

contrast, the lung is an excellent target for the direct administration of anti-sense oligonucleotides, and provides a non-invasive and a tissue-specific route. The delivery of anti-sense agents to the lung has been relatively undeveloped.

Adenosine may constitute an important mediator in the lung for various diseases, including bronchial asthma. Its potential role was suggested by the finding that asthmatics respond favorably to aerosolized adenosine with marked bronchoconstriction whereas normal individuals do not. An asthmatic rabbit animal model, the dust mite allergic rabbit model for human asthma, responded in a similar fashion to aerosolized adenosine with marked bronchoconstriction whereas non-asthmatic rabbits showed no response. More recent work with this animal model suggested that adenosine-induced bronchoconstriction and bronchial hyperresponsiveness in asthma may be mediated primarily through the stimulation of adenosine receptors. Adenosine has also been shown to cause adverse effects, including death, when administered therapeutically for other diseases and conditions in subjects with previously undiagnosed hyper reactive airways.

A handful of medicaments have been available for the treatment of respiratory diseases and conditions, although in general they all have limitations. Theophylline, an important drug in the treatment of asthma, is a known adenosine receptor antagonist which was reported to eliminate adenosine-mediated bronchoconstriction in asthmatic rabbits. A selective adenosine A<sub>1</sub> receptor antagonist, 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX) was also reported to inhibit adenosine-mediated bronchoconstriction and bronchial hyperresponsiveness in allergic rabbits. The therapeutic and preventative applications of currently available adenosine A<sub>1</sub> receptor-specific antagonists are, nevertheless, limited by their toxicity. Theophylline, for example, has been widely used in the treatment of asthma, but is associated with frequent, significant toxicity resulting from its narrow therapeutic dose range. DPCPX is far too toxic to be useful clinically. The fact that, despite decades of extensive research, no specific adenosine receptor antagonist is available for clinical use attests to the general toxicity of these agents.

Anti-sense oligonucleotides have received considerable theoretical consideration for their potential use as pharmacological agents in human disease. Finding practical and effective applications of these agents in actual models of human disease, however, have been few and far between, particularly because they had to be administered in large doses. Another important consideration in the pharmacologic application of these molecules is their route of administration. Many in vivo applications have involved the direct administration of anti-sense oligonucleotides to limited regions of the brain. Such applications, however, have limited clinical utility due to their invasive nature.

The systemic administration of anti-sense oligonucleotides as pharmacological agents



has been found to have also significant problems, not the least of which being a difficulty in targeting disease-involved tissues. That is, the necessary dilution of the anti-sense oligonucleotide in the circulatory system makes extremely difficult to attain a therapeutic dose at the target tissue by intravenous or oral administration. The bioavailability of orally administered anti-sense oligonucleotides is very low, of the order of less than about 5%.

Anti-sense oligonucleotides have been used in therapy by many, including the present inventor, who in his previous work successfully treated various diseases and conditions by direct administration of these agents to the lung. In many instances, other workers have had to face the difficulties associated with the delivery of DNA molecules to a desired target. Thus, the route of administration may be of extreme importance for treating generalized diseases and conditions as well as those which are localized.

Accordingly, there is a need for effective ways to implement anti-sense therapy, particularly those which are highly effective for the treatment of diseases and conditions which are of a complex nature. Examples of the latter are those diseases and conditions which are associated with complex pathways and multiple endogenous agents which either alone, or in combination with one another, result in pathological conditions to the subject.

#### SUMMARY OF THE INVENTION

This invention relates to an agent, comprising an anti-sense oligonucleotide hybridizing to two or more mRNAs, or multiple target anti-sense oligos (MTA oligos), such as those that correspond to target genes, genomic flanking regions, the initiation codon, intron-exon borders, and the like, and the entire sequence of RNAs, including the coding region of mRNA and non-coding RNA segments such as the 5' cap or end and the 3' end, e.g. poly-A segment, and RNAs encoding proteins known to be associated with one or more diseases or conditions and mixtures thereof. The mRNAs, for example, may encode polypeptide(s) such as transcription factors, stimulating and activating factors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensins, growth factors, vasoactive peptides and receptors, and binding proteins; or those mRNA which correspond to an oncogene. The present agent contains less than or about 15% adenosine (A), and in many cases is completely devoid of adenosine, and is also presented as a composition, which may be in the form of a capsule or cartridge, various formulations, and a kit provided with a delivery device and instructions for its use. ~~The anti-sense-oligos of the invention may have their adenosine content reduced by substitution with an adenosine-like binding substitute such as universal base.~~

The kit may also have other therapeutic agents, and ingredients for the composition. The agent also may be provided operatively linked to a vector and/or in a transfected host cell.

The agent, composition and formulation of the invention may be applied to the treatment of a disease or condition associated with the presence of an mRNA corresponding to at least one target gene, genomic flanking regions or proteins, by administration to a subject afflicted with the disease or condition of an amount of the MTA oligo of this invention effective to reduce the production or availability, or to increase the degradation, by the subject of at least one of the target mRNA. In a preferred embodiment, the agent may be administered in an amount effective to reduce the production or availability, or to increase the degradation of at least two of the target mRNAs. Typical diseases and conditions of this invention are those associated with impaired respiration and inflammation, including lung diseases, ailments and conditions that have a negative effect on the lungs of a subject. Examples of diseases and conditions, which may be treated preventively, prophylactically and therapeutically with the agent of this invention, are pulmonary vasoconstriction, inflammation, allergic rhinitis, acute asthma, allergies, asthma, impeded respiration, respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers such as leukemias, lymphomas, carcinomas, and the like, e.g. colon cancer, breast cancer, ~~lung cancer~~ pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer. The present agent(s) is (are) also suitable for administration before, during and after other treatments, including radiation, chemotherapy, antibody therapy, phototherapy and cancer, and other types of surgery. Alternatively, the present agent may be effectively administered preventively, prophylactically or therapeutically, and in conjunction with other therapies, or by itself for conditions without known therapies or as a substitute for therapies that have significant negative side effects.

The composition of this invention may be administered by transdermal or systemic routes, including by, but not exclusively, oral, intracavitary, intranasal, intraanal, intravaginal, transdermal, intradermal, intrabuccal, intravenous, subcutaneous, intramuscular, intratumor, intraglandular, by inhalation, intraarterial, intravascular in general, into the ear, intracranial, intrathecal, intraorgan including via a shunt to, for example, the liver or other organs, by implantation and intraocular administration to a human or any other animal, including vertebrates, such as mammals. The treatment of this invention may be prophylactic or therapeutic. In a preferred embodiment, the present agents are administered directly into the respiratory system of a subject, so that the agent has direct access to the lungs, in an amount effective to reduce or inhibit the effect in the lung of the targeted diseases or conditions.

The agent of this invention may be produced by selecting two or more targets such as genes, genomic flanking regions, intron-exon borders, and the like, or the entire sequence of RNAs, including non-coding RNAs, and RNAs encoding proteins known to be associated with at least one disease or condition; obtaining RNAs selected from the group consisting of RNAs corresponding to the genes and genomic flanking regions, and RNAs encoding the target proteins; selecting a segment of a first RNA which is at least about 60%, preferably about 80%, and still more preferably about 90% and even about 100% homologous to a segment of at least a segment of a second RNA; and synthesizing one or more anti-sense oligonucleotide(s) to the one or more RNA segments. The target RNA includes every segment of precursor and spliced mRNAs and other RNA molecules, including the 5'- and 3'-ends, and the coding portions as well as overlapping segments juxtaposed over the coding and non-coding sequences. In a preferred form of the invention, the two or more targets may be located in the same molecule. For instance, in the case of a mRNA encoding a protein with multiple subunits, MTA oligos may be found in segments of the RNA which encode different protein subunits. Also provided are MTA oligos which are produced by the method of the invention.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention arose from a desire by the inventor to improve on his own prior discovery, and those of others, that anti-sense oligonucleotides may be utilized therapeutically in the treatment of diseases or conditions which have multiple contributing pathways. The inventor reasoned that he could improve on his prior success in attenuating or enhancing the effects of one specific pathway by designing anti-sense oligonucleotides directed to a specific target associated with a disease or condition. He, thus, set out to attempt a novel and unobvious strategy directed to multiple targets. In so doing, he overcame numerous obstacles, particularly the extensive searching and selection necessary to obtain targets as well as their locating the desired sequences, be it genomic DNA, RNAs or proteins involved in specific diseases. Thereafter, he exemplified the invention by application to some specific diseases or conditions, and provided various preferred embodiments and specifically designed multiple targeted anti-sense oligonucleotide (MTA oligo) sequences.

The multi-targeted anti-sense (MTA) oligonucleotides of this invention have the capacity to attenuate the expression of more than one target mRNA, or to enhance or attenuate the activity of one or more pathways. By means of example, the present method may be practiced by first identifying all possible desadenosine (desA) anti-sense sequences of about 7, about 10, about 12, about 15, about 18, about 21 to about 28, about 30, about 35, about 40, about 45, about 50, about 60 or more mononucleotides in a target mRNA. This may be attained by searching for segments that are 7 or more nucleotides long within a target sequence

which are low in, or lack, thymidine (T), a nucleotide which is complementary to adenosine (A). This search typically results in about 10 to 30 such desT segments, i. e. naturally lacking thymidine, or segments with low T content, e. g. up to and including about 15%T, from which anti-sense oligonucleotides of varying lengths may be designed for a typical target mRNA of average length, i. e. about 1800 nucleotides long. Thereafter, the sense sequence for each strictly complementary desA anti-sense sequence obtained for a specific target may be then deduced. The thus deduced sense sequence may be then used to search for sequences of preferred secondary targets. Alternatively, one or more sequence data bases, e. g., GENBANK, and the like, may be searched for alternative secondary sequences. Thus, the targeting may be undertaken in several manners, one being the selection of specific targets associated with one or more related diseases. Alternatively, a primary target may be selected first, and an anti-sense oligonucleotide found, preferably a desA oligonucleotide and, then, secondary, tertiary or more targets searched for. In a typical search, either the list of preferred secondary targets or of a data base, multiple instances of homologous secondary targets of interest are identified. That is, the present technology is directed to finding the instances where there are natural homologies between primary, secondary, and greater sequences, and utilizing the finding for the therapeutic treatment of specific diseases or conditions associated with the target macromolecules from which the MTAs are obtained.

The present technology relies on the design of anti-sense oligos targeted to mRNAs associated with ailments involving lung airway pathology(ies), and on their modification to reduce the occurrence of undesirable side effects caused by their release of adenosine upon breakdown, while preserving their activity and efficacy for their intended purpose. In this manner, the inventor targets a specific gene to design one or more anti-sense oligonucleotide(s) (oligos) that selectively bind(s) to the corresponding mRNA, and then reduces, if necessary, their content of adenosine via substitution with universal base or an adenosine analog incapable of activating adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptors. Based on his prior experience in the field, the inventor reasoned that in addition to "downregulating" specific genes, he could increase the effect of the agent(s) administered by either selecting segments of RNA that are devoid, or have a low content, of thymidine (T) or, alternatively, substitute one or more adenosine(s) present in the designed oligonucleotide(s) with other nucleotide bases, so called universal bases, which bind to thymidine but lack the ability to activate adenosine receptors and otherwise exercise the constricting effect of adenosine in the lungs, etc. Given that adenosine (A) is a nucleotide base complementary to thymidine (T), when a T appears in the RNA, the anti-sense oligo will have an A at the same position. For consistency's sake, all RNAs and oligonucleotides are represented in this patent by a single strand in the 5' to 3' direction, when read from left to right, although their complementary sequence(s) is (are) also encompassed

within the four corners of the invention. In addition, all nucleotide bases and amino acids are represented utilizing the recommendations of the IUPAC-IUB Biochemical Nomenclature Commission, or by the known 3-letter code (for amino acids).

5 The method of the present invention may be used to treat ailments associated with reduced airway function in a subject, whatever its cause. The adenosine content of the anti-sense agent(s) of the invention have a reduced A content to prevent its liberation upon in vivo degradation of the agent(s). Examples of airway diseases that may be treated by the method of the present invention include cystic fibrosis, asthma, pulmonary hypertension and vasoconstriction, chronic obstructive pulmonary disease (COPD), chronic bronchitis,  
10 respiratory distress syndrome, lung cancer and lung metastatic cancers and other airway diseases, including those with inflammatory response.

Anti-sense oligos to the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> receptors, CCR3 (chemokine receptors), bradykinin 2B, CAM (vascular cell adhesion molecule), and eosinophil receptors, among others, have been shown to be effective in down-regulating the expression of their  
15 genes. Some of these act to alleviate the symptoms or reduce respiratory ailments and/or inflammation, for example, by "down regulation" of the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and/or A<sub>3</sub> receptors and CCR3, bradykinin 2B, VCAM (vascular cell adhesion molecule) and eosinophil receptors. These agents are preferably administered directly into the respiratory system, e.g., by inhalation or other means, so that they may reach the lungs without widespread systemic  
20 dissemination. This permits the use of substantially lower doses of the agent of the invention as compared with those administered by the prior art, systemically or by other generalized routes and, consequently, reduce undesirable side effects resulting from the agent's widespread distribution in the body. The agent(s) of this invention has (have) been shown to reduce the amount of receptor protein expressed by the tissue. These agents, thus, rather than merely  
25 interacting with their targets, e.g. a receptor, lower the number of target proteins that other drugs may interact with. In this manner, the present agent(s) afford(s) extremely high efficacy with low toxicity.

The adenosine receptors discussed above are mere examples of the high power of the inventor's technology. In fact, a large number of genes may be targeted in a similar manner  
30 by the present agent(s), to reduce or down-regulate protein expression. By means of example, if the target disease or condition is one associated with impeded or reduced breathing, bronchoconstriction, chronic bronchitis, pulmonary bronchoconstriction and/or hypertension, chronic obstructive pulmonary disease (COPD), allergy, asthma, cystic fibrosis, respiratory distress syndrome, cancers, which either directly or by metastasis afflict the lung, the present  
35 method may be applied to a list of potential target mRNAs, which includes the targets listed in Table 1 below, among others.

**Table 1: Pulmonary Disease or Condition (Asthma/Inflammation) Targets**

	NfκB Transcription Factor	Interleukin-8 Receptor (IL-8 R)
	Interleukin-5 Receptor (IL-5R)	Interleukin-4 Receptor (IL-4R)
5	Interleukin-3 Receptor (IL-3R)	Interleukin-1β (IL-1β)
	Interleukin-1β Receptor (IL-1βR)	Eotaxin
	Tryptase	Major Basic Protein
	β2-adrenergic Receptor Kinase	Endothelin Receptor A
	Endothelin Receptor B	Preproendothelin
10	Bradykinin B2 Receptor (B2BR)	IgE (High Affinity Receptor)
	Interleukin-1 (IL-1)	Interleukin 1 Receptor (IL-1 R)
	Interleukin-9 (IL-9)	Interleukin-9 Receptor (IL-9 R)
	Interleukin-11 (IL-11)	Interleukin-11 Receptor (IL-11 R)
	Inducible Nitric Oxide Synthase	Cyclooxygenase (COX)
15	Intracellular Adhesion Molecule 1 (ICAM-1)	Vascular Cellular Adhesion Molecule (VCAM)
	Rantes	Endothelial Leukocyte Adhesion Molecule (ELAM-1)
	Cyclooxygenase-2 (COX-2)	GM-CSF, Endothelin-1
	Monocyte Activating Factor	Neutrophil Chemotactic Factor
	Neutrophil Elastase	Defensin 1,2,3
20	Muscarinic Acetylcholine Receptors	Platelet Activating Factor
	Tumor Necrosis Factor α	5-lipoxygenase
	Phosphodiesterase IV	Substance P
	Substance P Receptor	Histamine Receptor
	Chymase	CCR-1 CC Chemokine Receptor
25	Interleukin-2 (IL-2)	Interleukin-4 (IL-4)
	Interleukin-12 (IL-12)	Interleukin-5 (IL-5)
	Interleukin-6 (IL-6)	Interleukin-7 (IL-7)
	Interleukin-8 (IL-8)	Interleukin-12 Receptor (IL-12R)
	Interleukin-7 Receptor (IL-7R)	Interleukin-1 (IL-1)
30	Interleukin-14 Receptor (IL-14R)	Interleukin-14
	CCR-2 CC Chemokine Receptor	CCR-3 CC Chemokine Receptor
	CCR-4 CC Chemokine Receptor	CCR-5 CC Chemokine Receptor
	Prostanoid Receptors	GATA-3 Transcription Factor
	Neutrophil Adherence Receptor	MAP Kinase
35	Interleukin-15 (IL-15)	Interleukin-15 Receptor (IL-15R)
	Interleukin-11 (IL-11)	Interleukin-11 Receptor (IL-11R)
	NFAT Transcription Factors	STAT 4

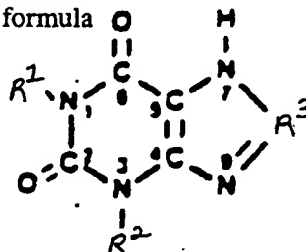
**Table 1: Pulmonary Disease or Condition (Asthma/Inflammation) Targets (Cont'd)**

	MIP-1 $\alpha$	MCP-2
	MCP-3	MCP-4
5	Cyclophilin (A, B, etc.)	Phospholipase A2
	Basic Fibroblast Growth Factor	Metalloproteinase
	CSBP/p38 MAP Kinase	Tryptase Receptor
	PDG2	Interleukin-3 (IL-3)
	Interleukin-10 (IL-10)	Cyclosporin A - Binding Protein
10	FK506-Binding Protein	$\alpha$ 4 $\beta$ 1 Selectin
	Fibronectin	$\alpha$ 4 $\beta$ 7 Selectin
	cMad CAM-1	LFA-1 (CD11a/CD18)
	PECAM-1	LFA-1 Selectin
	C3bi	PSGL-1
15	E-Selectin	P-Selectin
	CD-34	L-Selectin
	p150,95	Mac-1 (CD11b/CD18)
	Fucosyl transferase	VLA-4
	CD-18/CD11a	CD11b/CD18
20	ICAM2 and ICAM3	C5a
	CCR3 (Eotaxin Receptor)	CCR1, CCR2, CCR4, CCR5
	LTB-4	AP-1 Transcription Factor
	Protein kinase C	Cysteinyl Leukotriene Receptor
	Tachykinin Receptors (tach R)	I $\kappa$ B Kinase 1 & 2
25	Interleukin-2 Receptor (IL-2R)	(e.g., Substance P, NK-1 & NK-3 Receptors)
	STAT 6	c-mas
	NF-Interleukin-6 (NF-IL-6)	Interleukin-10 Receptor (IL-10R)
	Interleukin-3 (IL-3)	Interleukin-2 Receptor (IL-2R)
	Interleukin-13 (IL-13)	Interleukin-12 Receptor (IL-12R)
30	Interleukin-14 (IL-14)	Interleukin-6 Receptor (IL-6R)
	Interleukin-16 (IL-16)	Interleukin-13 Receptor (IL-13R)
	Medullasin	Interleukin-16 Receptor (IL-16R)
	Adenosine A <sub>1</sub> Receptor (A <sub>1</sub> R)	Tryptase-I
	Adenosine A <sub>2b</sub> Receptor (A <sub>2b</sub> R)	Adenosine A <sub>3</sub> Receptor (A <sub>3</sub> R)
35	$\beta$ Tryptase	
	Adenosine A <sub>2a</sub> Receptor (A <sub>2a</sub> R)	IgE Receptor $\beta$ Subunit (IgE R $\beta$ )
	Fc-epsilon receptor CD23 antigen	IgE Receptor $\alpha$ Subunit (IgE R $\alpha$ )
	IgE Receptor Fc Epsilon Receptor (IgERFc $\xi$ R)	Substance P Receptor
	Histidine decarboxylase	Tryptase-I
40	Prostaglandin D Synthase	Eosinophil Cationic Protein
	Eosinophil Derived Neurotoxin	Eosinophil Peroxidase
	Endothelial Nitric Oxide Synthase	Endothelial Monocyte Activating Factor
	Neutrophil Oxidase Factor	Cathepsin G
	Macrophage Inflammatory Protein-1-	Interleukin-8 Receptor $\alpha$ Subunit (IL-8 R $\alpha$ )
45	Alpha/Rantes Receptor	Substance P
	Endothelin Receptor ET-B	Endothelin ETA Receptor

The oligos of this invention may be obtained by first selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C, and then obtaining a first oligonucleotide 4 to 60 nucleotides long which comprises the selected fragment and has a C and G nucleic acid content of up to and including about 15%. The latter step may be conducted by obtaining a second oligonucleotide 4 to 60 nucleotides long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an adenosine base content of up to and including about 15%. This method may also comprise, when the selected fragment comprises at least one thymidine base,

substituting an adenosine base in the corresponding nucleotide of the anti-sense fragment with ~~a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.5 of the adenosine base agonist activity at the adenosine-A<sub>1</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors,~~ and heteroaromatic bases which

- 5 have no activity or have an agonist activity at the adenosine A<sub>2a</sub> receptor. The analogue heteroaromatic bases may be selected from all pyrimidines and purines, which may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, 10 arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH<sub>2</sub>, primary, secondary and tertiary amine, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, cycloalkyl, heterocycloalkyl and heteroaryl. The pyrimidines and purines may be substituted at all positions as is known in the art, but preferred are those which are substituted 15 at positions 1, 2, 3, 4, 7 and/or 8. More preferred are pyrimidines and purines such as theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula



- wherein R<sup>1</sup> and R<sup>2</sup> are independently H, alkyl, alkenyl or alkynyl and R<sup>3</sup> is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH<sub>2</sub>-alkylamino-ketoxyalkyloxy-aryl, mono and 20 dialkylaminoalkyl-N-alkylamino-SO<sub>2</sub> aryl, among others.

- When no segments having the desired T content were found or where desirable segments contained T, the inventor proposed to reduce the adenosine content of the anti-sense oligos corresponding to the thymidines (T) present in the target RNA to less than about 15%, 25 or fully eliminated A from the oligonucleotide sequence as a means for preventing their breakdown products from freeing adenosine into the lung tissue environment and, thereby, aggravating the subject's ailment and/or countering the beneficial effect of the administered agent.

- By means of example, the NFκB transcription factor may be selected as a primary target 30 and searched for desthymidine (desT) segments. When a number of desT segments are found,



the anti-sense segments may be deduced, and perhaps about 20 or even more desA anti-sense sequences obtained. These anti-sense sequences represent, when possible, all desA anti-sense sequences found within the mRNA of this primary target, and may be utilized to start the search for homologous sequences within a preferred list of secondary targets such as the one shown in Table 1 above or Table 2 below, or within a sequence data base, such as GENBANK. For each of the about 20 original desA anti-sense sequences found for NF $\kappa$ B transcription factor, typically about 10 to 30 homologous sequences may be found among the other members of the group shown in Table 1 above (secondary, tertiary, and the like targets). In some instances, the search produces a homology for the primary target with, not only secondary targets (homology between primary target and sequence from one other target mRNA), but with tertiary targets (homology between primary target and sequences from, e. g. three other target mRNA), as well. The latter case, however, is more rare. When this occurs, the anti-sense oligos found are said to be 100% homologous. More typically, however, the sequences found contain some non-fully homologous nucleotides within the secondary or tertiary or quaternary sequences. In many cases, this mismatch would suffice to render the anti-sense oligonucleotide less active or even inactive against the target(s). In some instances, the presence of even one non-homologous nucleotide may be sufficient to reduce the activity of an anti-sense oligonucleotide. When the so called "homologous" sequences obtained have mismatches, acceptable are up to about 40%, preferably no more than about 30%, more preferable no more than 20%, still more preferable no more than 10% mismatched nucleotides. In some instances the higher % mismatches are acceptable, and the oligos still are active since the non-homologous nucleotide may be "fixed" or replaced with a "Universal" base that may base-pair with similar or equal affinity with two or more of the four nucleotide present in natural DNA: A, G, C, and T. This "fixing" step generates a further novel sequence, different from the one found in nature, that permits the anti-sense oligonucleotide to bind, preferably equally well, with the primary target, the secondary target, the tertiary target, etc.

As the NF $\kappa$ B transcription factor is selected as a target, its mRNA or DNA are searched for low thymidine (T) or desthymidine (desT) fragments. Only desT segments of the mRNA or DNA are selected which, in turn, will produce desA anti-sense as their complementary strand. When a number of RNA desT segments are found, the sequence of the anti-sense segments may be deduced. Typically, about 10 to 30 and even larger numbers of desA anti-sense sequences may be obtained. These anti-sense sequences may include some or all desA anti-sense oligonucleotide sequences corresponding to desT segments of the mRNA of the target, such as anyone of those shown in Table 1 above or Table 2 below. When this occurs, the anti-sense oligonucleotides found are said to be 100% A-free. For each of the original desA anti-sense oligonucleotide sequences corresponding to the target gene, e.g. the NF $\kappa$ B

transcription factor, typically about 10 to 30 sequences may be found within the target gene or RNA which have a low content of thymidine (RNA). In accordance with this invention, the selected fragment sequences may also contain a small number of thymidine (RNA) nucleotides within the secondary or tertiary or quaternary sequences. In some cases, a large adenosine content may suffice to render the anti-sense oligonucleotide less active or even inactive against the target. In accordance with this invention, these so called "non-fully desA" sequences may preferably have a content of adenosine of less than about 15%, more preferably less than about 10%, and still more preferably less than 5%, and some even less than 2% adenosine. In some instances a higher content of adenosine is acceptable and the oligonucleotides are still active, particularly where the adenosine nucleotide may be "fixed" or replaced with a "Universal" base that may base-pair with similar or equal affinity to two or more of the four nucleotide present in natural DNA: A, G, C, and T. A universal base is defined in this patent as any compound, more commonly an adenosine analogue, having the capacity to hybridize to thymidine, preferably having substantially reduced, or substantially lacking, ability to bind adenosine receptors. Alternatively, adenosine analogs which do not activate adenosine receptors, such as the adenosine A<sub>1</sub>, A<sub>2</sub>, and/or A<sub>3</sub> receptors, most preferably A<sub>1</sub> receptors, may be used. One example of a universal base is  $\alpha$ -deoxyribofuranosol-(5-nitroindole), and an artisan will know how to select others. This "fixing" step generates a further novel sequence, different from the one found in nature, that permits the anti-sense oligonucleotide to bind, preferably equally well, with the target RNA. An example of a universal base is 3-deoxyribosyl-(5-nitroindole). Other examples of universal bases are 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one and 2-amino-6-methoxyaminopurine. In addition to the above, Universal bases which may be substituted for any other base although with somewhat reduced hybridization potential, include 3-nitropyrrole 2'-deoxynucleoside 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine and 2'-deoxynebularine (Glen Research, Sterling, VA). More specific mismatch repairs may be made using "P" nucleotide, 6H, 8H-3, 4-dihydropyrimido[4,5-c] [1,2] oxazin-7-one, which base pairs with either guanine (G) or adenine (A) and "K" nucleotide, 2-amino-6-methoxyaminopurine, which base pairs with either cytidine (C) or thymidine (T), among others. Others which are known in the art are also suitable. See, for example, Loakes, D. and Brown, D. M., Nucl. Acids Res. 22:4039-4043 (1994); Ohtsuka, E. et al., J. Biol. Chem. 260(5):2605-2608 (1985); Lin, P.K.T. and Brown, D. M., Nucleic Acids Res. 20(19):5149-5152 (1992); Nichols, R. et al., Nature 369(6480): 492-493 (1994); Rahmon, M. S. and Humayun, N. Z., Mutation Research 377 (2): 263-8 (1997); Amosova, O., et al., Nucleic Acids Res. 25 (10): 1930-1934 (1997); Loakes D. & Brown, D. M., Nucleic

Acids Res. 22 (20): 4039-4043 (1994), the entire sections relating to universal bases and their preparation and use in nucleic acid binding is incorporated herein by reference.

When non-fully desT sequences are found in the naturally occurring target, they typically are selected so that ~~about 1 to 3 universal base substitutions~~ will suffice to obtain a 100% "desA" anti-sense oligonucleotide. Thus, the present method provides either anti-sense oligonucleotides to different targets which are low in, or devoid of, A content, as well as anti-sense oligonucleotides where one or more adenosine nucleotides, ~~e.g. about 1 to 3, or more,~~ may be "fixed" by replacement with a "Universal" base. Universal bases are known in the art and need not be listed herein. An artisan will know which bases may act as universal bases, and replace them for A.

The present approach to the design of anti-sense oligonucleotide approach is also applicable to a variety of other diseases or conditions, including other inflammatory diseases, such as cystic fibrosis, chronic obstructive pulmonary disease, chronic bronchitis, pulmonary hypertension, cancers, including those which metastasize to the lung, such as breast cancer, colon cancer, respiratory distress syndrome, prostate cancer, pancreatic cancer, kidney cancer, lymphomas, melanomas, hepatocellular carcinomas, etc.

As used herein, the term "treat" or "treating" asthma or other respiratory and inflammatory conditions or diseases refers to a treatment which decreases the likelihood that the subject administered such treatment will manifest symptoms of a respiratory or inflammatory lung disease or other lung conditions. The term "down-regulate" refers to inducing a decrease in production, secretion or availability (and thus a decrease in concentration) of the targeted intracellular protein.

The present invention is concerned primarily with the treatment of vertebrates, and within this group, of mammals, including human and non-human simians, wild and domesticated animals, marine and land animals, household pets, and zoo animals, for example, felines, canines, equines, pachiderms, cetaceans, and still more preferably to human subjects. One particularly suitable application of this technology is for veterinary purposes, and includes all types of small and large animals in the care of a veterinarian, including wild animals, marine animals, household animals, zoo animals, and the like. Targeted genes and proteins are preferably mammalian, and the sequences targeted are preferably of the same species as the subject being treated. Although in many instances, targets of a different species are also suitable, particularly those segments of the target RNA or gene that display greater than about 45% homology, preferably greater than about 85% homology, still more preferably greater than about 95% homology, with the recipient's sequence. A preferable group of agents is composed of des-A anti-sense oligos. Another preferred group is composed of non-fully desA oligonucleotides, where one or more adenosine bases are replaced with universal bases.

The terms "anti-sense" oligonucleotides generally refers to small, synthetic oligonucleotides, resembling single-stranded DNA, which in this patent are applied to the inhibition of gene expression by inhibition of a target messenger RNA (mRNA). See, Milligan, J. F. et al., J. Med. Chem. 36(14), 1923-1937 (1993), the relevant portion of which is hereby incorporated in its entirety by reference. The present agents inhibit gene expression of target genes, such as those of the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, or A<sub>3</sub> receptors, CCR3 (chemical receptor 320, also known as the eotaxin receptor), VCAM (vascular cell adhesion molecule), eosinophil receptor, bradykinin 2B receptor, and many others listed in Table 1 above. This is generally attained by hybridization of the anti-sense oligonucleotides to coding (sense) sequences of a targeted messenger RNA (mRNA), as is known in the art. The exogenously administered agents of the invention decrease the levels of mRNA and protein encoded by the target gene and/or cause changes in the growth characteristics or shapes of the thus treated cells. See, Milligan et al. (1993); Helene, C. and Toulme, J. Biochim. Biophys. Acta 1049, 99-125 (1990); Cohen, J. S. D., Ed., Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression; CRC Press: Boca Raton, FL (1987), the relevant portion of which is hereby incorporated in its entirety by reference. As used herein, "anti-sense oligonucleotide" is generally a short sequence of synthetic nucleotide that (1) hybridizes to any segment of a mRNA encoding a targeted protein under appropriate hybridization conditions, and which (2) upon hybridization causes a decrease in gene expression of the targeted protein.

The terms "des-adenosine" (desA) and "des-thymidine" (desT) refer to oligonucleotides substantially lacking either adenosine (desA) or thymidine (desT). In some instances, the des T sequences are naturally occurring, and in others they may result from substitution of an undesirable nucleotide (A) by another one lacking its undesirable activity. In the present context, the substitution is generally accomplished by substitution of A with a "universal base", as is known in the art.

The mRNA sequence of the targeted protein may be derived from the nucleotide sequence of the gene expressing the protein. For example, the sequence of the genomic human adenosine A<sub>1</sub> receptor and that of the rat and human adenosine A<sub>3</sub> receptors are known. See, US Pat. No. 5,320,962; Zhou, F., et al., Proc. Nat'l Acad. Sci. (USA) 89 :7432 (1992); Jacobson, M.A., et al., U.K. Pat. Appl. No. 9304582.1. The sequence of the adenosine A<sub>2b</sub> receptor gene is also known. See, Salvatore, C. A., Luneau, C. J., Johnson, R. G. and Jacobson, M., Genomics (1995), the relevant portion of which is hereby incorporated in its entirety by reference. The sequences of many of the exemplary target genes are also known. See, GenBank, NIH. The sequences of those genes whose sequences are not yet available may be obtained by isolating the target segments applying technology known in the art. Once the sequence of the gene, its RNA and/or the protein are known, an anti-sense oligonucleotides

may be produced according to this invention as described above to reduce the production of the targeted protein in accordance with standard techniques.

5 In one aspect of this invention, the anti-sense oligonucleotide has a sequence which specifically binds to a portion or segment of an mRNA molecule which encodes a protein associated with a disease or condition associated with impeded breathing, lung inflammation, airway obstruction, bronchitis, and the like. One effect of this binding is to reduce or even prevent the translation of the corresponding mRNA and, thereby, reduce the available amount of target protein in the subject's lung.

10 In one preferred embodiment of this invention, the phosphodiester residues of the anti-sense oligonucleotide are modified or substituted. Chemical analogs of oligonucleotides with modified or substituted phosphodiester residues, e.g., to the methylphosphonate, the phosphotriester, the phosphorothioate, the phosphorodithioate, or the phosphoramidate, which increase the in vivo stability of the oligonucleotide are particularly preferred. The naturally occurring phosphodiester linkages of oligonucleotides are susceptible to some degree of  
15 degradation by cellular nucleases. Many of the residues proposed herein, on the contrary, are highly resistant to nuclease degradation. See Milligan et al., and Cohen, J. S. D., *supra*. In another preferred embodiment of the invention, the oligonucleotides may be protected from degradation by adding a "3'-end cap" by which nuclease-resistant linkages are substituted for phosphodiester linkages at the 3' end of the oligonucleotide. See, Tidd, D. M. and Warenius, H.M., *Be. J. Cancer* 60: 343-350 (1989); Shaw, J.P. et al., *Nucleic Acids Res.* 19: 747-750 (1991), the relevant section of which are incorporated in their entireties herein by reference. Phosphoramidates, phosphorothioates, and methylphosphonate linkages all function adequately in this manner for the purposes of this invention. The more extensive the modification of the phosphodiester backbone the more stable the resulting agent, and in many instances the higher  
25 their RNA affinity and cellular permeation. See Milligan, et al., *supra*. Thus, the number of residues which may be modified or substituted will vary depending on the need, target, and route of administration, and may be from 1 to all the residues, to any number in between. Many different methods for replacing the entire phosphodiester backbone with novel linkages are known. See, Millikan et al, *supra*. Preferred backbone analogue residues include  
30 phosphorothioate, methylphosphonate, phosphotriester, thioformacetal, phosphorodithioate, phosphoramidate, formacetal boranophosphate, 3'-thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite., 2'-O methyl, sulfoxide, sulfide, hydroxylamine, methylene(methylimino) (MMI), and methyleneoxy(methylimino) (MOMI) residues. Phosphorothioate and methylphosphonate-  
35 modified oligonucleotides are particularly preferred due to their availability through automated oligonucleotide synthesis. See, Millikan et al, *supra*. Where appropriate, the agent of this

invention may be administered in the form of their pharmaceutically acceptable salts, or as a mixture of the anti-sense oligonucleotide and its salt. In another embodiment of this invention, a mixture of different anti-sense oligonucleotides or their pharmaceutically acceptable salts is administered.

5           The agents of this invention have the capacity to attenuate the expression of one target mRNA and/or to enhance or attenuate the activity of one pathway. By means of example, the present method may be practiced by identifying all possible deoxyribonucleotide segments which are low in thymidine (T) or deoxynucleotide segments low in adenosine (A) of about 7 or more mononucleotides, preferably up to about 60 mononucleotides, more preferably about 10 to about 36 mononucleotides, and still more preferably about 12 to about 21 mononucleotides, in a target mRNA or a gene, respectively. This may be attained by searching for mononucleotide segments within a target sequence which are low in, or lack thymidine (RNA), a nucleotide which is complementary to adenosine, or that are low in adenosine (gene), that are 7 or more nucleotides long. In most cases, this search typically results in about 10 to 15 30 such sequences, i. e. naturally lacking or having less than about 40% adenosine, anti-sense oligonucleotides of varying lengths for a typical target mRNA of average length, i. e., about 1800 nucleotides long. Those with high content of T or A, respectively, may be fixed by substitution of a universal base for one or more As.

          The agent(s) of this invention may be of any suitable length, including but not limited to, about 7 to about 60 nucleotides long, preferably about 12 to about 45, more preferably up to about 30 nucleotides long, and still more preferably up to about 21, although they may be of other lengths as well, depending on the particular target and the mode of delivery. The agent(s) of the invention may be directed to any and all segments of a target RNA. One preferred group of agent(s) includes those directed to an mRNA region containing a junction between an intron and an exon. Where the agent is directed to an intron/exon junction, it may either entirely overlie the junction or it may be sufficiently close to the junction to inhibit the splicing-out of the intervening exon during processing of precursor mRNA to mature mRNA, e.g. with the 3' or 5' terminus of the anti-sense oligonucleotide being positioned within about, for example, within about 2 to 10, preferably about 3 to 5, nucleotide of the intron/exon junction. Also preferred are anti-sense oligonucleotides which overlap the initiation codon, and those near the 5' and 3' termini of the coding region.

          This multi-targeted anti-sense (MTA) oligonucleotide approach is, thus, applicable to a variety of other diseases or conditions, including other inflammatory diseases, such as cystic fibrosis, chronic obstructive pulmonary disease, chronic bronchitis, etc.. Other specific diseases or conditions to which this technology is effectively applied are pulmonary hypertension, and cancers.

Table 2 below provides a number of targets to which multi-targeted anti-sense (MTA) oligonucleotides are effectively applied. Others may also be targeted.

**Table 2: Cancer Targets**

5	Transforming Oncogenes	Therapy Targets
	ras	thymidylate synthetase
	src	thymidylate synthetase
10	myc	dihydrofolate reductase
	bcl-2	thymidine kinase
		deoxycytidine kinase
		ribonucleotide reductase

15 A group of preferred targets for the treatment of cancers are genes associated with different types of cancers, or those generally known to be associated with malignancies, whether they are regulatory or involved in the production of RNA and/or proteins. Examples are transforming oncogenes, including, but not limited to, ras, src, myc, and bcl-2, among others. Other targets are those to which present cancer chemotherapeutic agents are directed to, such as various enzymes, primarily, although not exclusively, thymidylate synthetase, 20 dihydrofolate reductase, thymidine kinase, deoxycytidine kinase, ribonucleotide reductase, and the like.

The present technology is extremely important for the treatment of diseases or conditions such as cancer given that traditional cancer therapies are fraught with the unresolved 25 problem of selectively killing cancer cells while preserving normal living cells from the devastating effects of treatments such as chemotherapy, radiotherapy, and the like. The present technology provides the ability of simultaneously attenuating or enhancing multiple pathways. This approach provides a significant advantage for the treatment of cancer because it permits the selection of a combination of multiple pathways, including primary, secondary and possibly 30 tertiary targets, which are not generally expressed simultaneously in normal cells. Thus, the present agent may be administered to a subject to cause a selective increase in toxicity within tumor cells that, for instance, express all three targets while normal cells that may express only one or two of the targets will be significantly less affected or even spared.

This invention thus provides an agent, comprising an anti-sense oligonucleotide to two 35 or more mRNAs selected from the group consisting of RNAs corresponding to target genes, to genomic flanking regions, the initiation origin, intron-exon borders, and the like, or the entire sequence of precursor RNAs, including the coding region of mRNAs, non-coding RNA

segments, the 5'-end and the 3'-end, e.g. poly-A segment and oligos targeted to the juxtaposition between coding and non-coding regions, and RNAs encoding proteins known to be associated with one or more diseases or conditions or mixtures thereof.

5 The agents administered in accordance with this invention are preferably designed to be anti-sense to target genes and/or mRNAs related in origin to the species to which it is to be administered. When treating humans, the agents are preferably designed to be anti-sense to a human gene or RNA. The agents of the invention encompass oligonucleotides which are anti-sense to naturally occurring DNA and/or RNA sequences, fragments thereof of up to a length of one (1) base less than the targeted sequence, preferably at least about 7 nucleotides long, 10 oligos having only over about 0.02%, more preferably over about 0.1%, still more preferably over about 1%, and even more preferably over about 4% adenosine nucleotides, and up to about 30%, more preferably up to about 15%, still more preferably up to about 10% and even more preferably up to about 5%, adenosine nucleotide, or lacking adenosine altogether, and oligos in which one or more of the adenosine nucleotides have been replaced with so-called 15 universal bases, which may pair up with thymidine nucleotides but fail to substantially trigger adenosine receptor activity. Examples of human sequences and fragments, which are not limiting, of anti-sense oligonucleotide of the invention are the following fragments as well as shorter segments of the fragments and of the full gene or mRNA coding sequences, exons and intron-exon junctions encompassing preferably 7, 10, 15, 18 to 21, 24, 27, 30, n-1 nucleotides 20 for each sequence, where n is the sequence's total number of nucleotides. These fragments may be selected from any portion of the longer oligo, for example, from the middle, 5'- end, 3'- end or starting at any other site of the original sequence. Of particular importance are fragments of low adenosine nucleotide content, that is, those fragments containing less than or about 30%, preferably less than or about 15%, more preferably less than or about 10%, and 25 even more preferably less than or about 5%, and most preferably those devoid of adenosine nucleotide, either by choice or by replacement with a universal base in accordance with this invention. The agent of the invention includes as a most preferred group sequences and their fragments where one or more adenosines present in the sequence have been replaced by a universal base (B), as exemplified here. Similarly, also encompassed are all shorter fragments 30 of the B-containing fragments designed by substitution of B(s) for adenosine(s) (A(s)) contained in the sequences, fragments thereof or segments thereof, as described above. A limited list of sequences and fragments is provided below.

Some of the examples of anti-sense oligonucleotide sequence fragments target the initiation codon of the respective gene, and in some cases adenosine is substituted with a 35 universal base adenosine analogue denoted as "B", which lacks ability to bind to the adenosine A<sub>1</sub> and/or A<sub>2</sub> receptors. In fact, such replacement nucleotide acts as a "spacer". Many of the



examples shown below provide one such sequence and many fragments overlapping the initiation codon, preferably wherein the number of nucleotides  $n$  is about 7, about 10, about 12, about 15, about 18, about 21 and up to about 28, about 35, about 40, about 50, about 60.

In one embodiment, at least one of the mRNAs to which the MTA oligo of the invention is targeted encodes a protein such as transcription factors, stimulating and activating factors, intracellular and extracellular receptors and peptide transmitters in general, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensins, growth factors, vasoactive peptides and receptors, and binding proteins, among others; or the mRNA is corresponding to an oncogene and other genes associated with various diseases or conditions.

Examples of target proteins are eotaxin, major basic protein, preproendothelin, eosinophil cationic protein, P-selectin, STAT 4, MIP-1 $\alpha$ , MCP-2, MCP-3, MCP-4, STAT 6, c-mas, NF-IL-6, cyclophilins, PDG2, cyclosporin A-binding protein, FK5-binding protein, fibronectin, LFA-1 (CD11a/CD18), PECAM-1, C3bi, PSGL-1, CD-34, substance P, p150,95, Mac-1 (CD11b/CD18), VLA-4, CD-18/CD11a, CD11b/CD18, C5a, CCR1, CCR2, CCR4, CCR5, and LTB-4, among others. Others are, however, suitable, as well.

In another embodiment, at least one of the mRNAs to which the MTA oligo is targeted encodes intracellular and extracellular receptors and peptide transmitters such as sympathomimetic receptors, parasympathetic receptors, GABA receptors, adenosine receptors, bradykinin receptors, insulin receptors, glucagon receptors, prostaglandin receptors, thyroid receptors, androgen receptors, anabolic receptors, estrogen receptors, progesterone receptors, receptors associated with the coagulation cascade, adenohipophyseal receptors, adenohipophyseal peptide transmitters, and histamine receptors (HisR), among others. However others are also contemplated.

The encoded sympathomimetic receptors and parasympathomimetic receptors include acetylcholinesterase receptors (AcChaseR) acetylcholine receptors (AcChR), atropine receptors, muscarinic receptors, epinephrine receptors (EpiR), dopamine receptors (DOPAR), and norepinephrine receptors (NEpiR), among others. Further examples of encoded receptors are adenosine A<sub>1</sub> receptor, adenosine A<sub>2</sub>B receptor, adenosine A<sub>3</sub> receptor, endothelin receptor A, endothelin receptor B, IgE high affinity receptor, muscarinic acetylcholine receptors, substance P receptor, histamine receptor, CCR-1 CC chemokine receptor, CCR-2 CC chemokine receptor, CCR-3 CC chemokine receptor (Eotaxin Receptor), interleukin-1 $\beta$  receptor (IL-1 $\beta$ R), interleukin-1 receptor (IL-1R), interleukin-1 $\beta$  receptor (IL-1 $\beta$ R), interleukin-3 receptor (IL-3R), CCR-4 CC chemokine receptor, cysteinyl leukotriene

receptors, prostanoid receptors, GATA-3 transcription factor receptor, interleukin-1 receptor (IL-1R), interleukin-4 receptor (IL-4R), interleukin-5 receptor (IL-5R), interleukin-8 receptor (IL-8R), interleukin-9 receptor (IL-9R), interleukin-11 receptor (IL-11R), bradykinin B2 receptor, sympathomimetic receptors, parasympathomimetic receptors, GABA receptors, adenosine receptors, bradykinin receptors, insulin receptors, glucagon receptors, prostaglandin receptors, thyroid receptors, androgen receptors, anabolic receptors, estrogen receptors, progesterone receptors, receptors associated with the coagulation cascade, adenohypophyseal receptors, and histamine receptors (HisR). Others are also contemplated even though not listed herein.

The encoded enzymes for development of the MTA oligos of the invention include synthetases, kinases, oxidases, phosphatases, reductases, polysaccharide, triglyceride, and protein hydrolases, esterases, elastases, and , polysaccharide, triglyceride, lipid, and protein synthases, among others. Examples of target enzymes are tryptase, inducible nitric oxide synthase, cyclooxygenase (Cox), MAP kinase, eosinophil peroxidase,  $\beta$ 2-adrenergic receptor kinase, leukotriene c-4 synthase, 5-lipoxygenase, phosphodiesterase IV, metalloproteinase, tryptase, CSBP/p38 MAP kinase, neutrophil elastase, phospholipase A2, cyclooxygenase 2 (Cox-2), fucosyl transferase, chymase, protein kinase C, thymidylate synthetase, dihydrofolate reductase, thymidine kinase, deoxycytidine kinase, and ribonucleotide reductase, among others. Any enzyme associated with a disease or condition , however, is suitable as a target for this invention.

Suitable encoded factors for application of this invention are, among others, Nf $\kappa$ B transcription factor, granulocyte macrophage colony stimulating factor (GM-CSF), AP-1 transcription factor, GATA-3 transcription factor, monocyte activating factor, neutrophil chemotactic factor, granulocyte/macrophage colony-stimulating-factor (G-CSF), NFAT transcription factors, platelet activating factor, tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ), and basic fibroblast growth factor (BFGF). Additional factors are also within the invention even though not specifically mentioned.

Suitable adhesion molecules for use with this invention include intracellular adhesion molecules 1 (ICAM-1), 2 (ICAM-2) and 3 (ICAM-3), vascular cellular adhesion molecule (VCAM), endothelial leukocyte adhesion molecule-1 (ELAM-1), neutrophil adherence receptor, mad CAM-1, and the like. Other known and unknown factors (at this time) may also be targeted herein.

Among the cytokines, lymphokines and chemokines preferred are interleukin-1 (IL-1), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-11 (IL-11), CCR-5 CC chemokine, and Rantes. Others, however, may also be targeted, as they are known to be involved in specific diseases

or conditions to be treated, or for their generic activities, such as inflammation.

Examples of defensins for the practice of this invention are defensin 1, defensin 2, and defensin 3, and of selectins are  $\alpha 4\beta 1$  selectin,  $\alpha 4\beta 7$  selectin, LFA-1 selectin, E-selectin, P-selectin, and L-selectin. Examples of oncogenes, although not an all inclusive list, are ras, src, myc, and bcl-2. Others, however, are also suitable for use with this invention.

The agents administered in accordance with this invention are preferably designed to be anti-sense to target genes and/or mRNAs related in origin to the species to which it is to be administered. When treating humans, the agents are preferably designed to be anti-sense to a human gene or RNA. The agents of the invention encompass oligonucleotides which are anti-sense to naturally occurring DNA and/or RNA sequences, fragments thereof of up to a length of one (1) base less than the targeted sequence, preferably at least about 7 nucleotides long, oligos having only over about 0.02%, more preferably over about 0.1%, still more preferably over about 1%, and even more preferably over about 4% adenosine nucleotides, and up to about 30%, more preferably up to about 15%, still more preferably up to about 10% and even more preferably up to about 5%, adenosine nucleotide, or lacking adenosine altogether, and oligos in which one or more of the adenosine nucleotides have been replaced with so-called universal bases, which may pair up with thymidine nucleotides but fail to substantially trigger adenosine receptor activity. Examples of human sequences and fragments, which are not limiting, of anti-sense oligonucleotide of the invention are the following fragments as well as shorter segments of the fragments and of the full gene or mRNA coding sequences, exons and intron-exon junctions encompassing preferably 7, 10, 15, 18 to 21, 24, 27, 30, n-1 nucleotides for each sequence, where n is the sequence's total number of nucleotides. These fragments may be selected from any portion of the longer oligo, for example, from the middle, 5'- end, 3'- end or starting at any other site of the original sequence. Of particular importance are fragments of low adenosine nucleotide content, that is, those fragments containing less than or about 30%, preferably less than or about 15%, more preferably less than or about 10%, and even more preferably less than or about 5%, and most preferably those devoid of adenosine nucleotide, either by choice or by replacement with a universal base in accordance with this invention. The agent of the invention includes as a most preferred group sequences and their fragments where one or more adenosines present in the sequence have been replaced by a universal base (B), as exemplified here. Similarly, also encompassed are all shorter fragments of the B-containing fragments designed by substitution of B(s) for adenosine(s) (A(s)) contained in the sequences, fragments thereof or segments thereof, as described above. A limited list of sequences and fragments is provided below.

Some of the examples of anti-sense oligonucleotide sequence fragments target the initiation codon of the respective gene, and in some cases adenosine is substituted with a

universal base adenosine analogue denoted as "B", which lacks ability to bind to the adenosine A<sub>1</sub> and/or A<sub>2</sub> receptors. In fact, such replacement nucleotide acts as a "spacer". Many of the examples shown below provide one such sequence and many fragments overlapping the initiation codon, preferably wherein the number of nucleotides n is about 7, about 10, about 12, about 15, about 18, about 21 and up to about 28, about 35, about 40, about 50, about 60.

#### Human Receptor-related Antisense Polynucleotide

5'-GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGGG C TGCTTTTCT TTTCTGGGCC  
TCTGTGGTCT GTTTTTTCT GGCCCTGCTG GGGCGCTCTC CGCCGCCCGC CTGGCTCCCG GBGCCCBTGB TGGGCBTGCC  
GTGGTCTTG CCCTCCTTG GCTGCCGTGC CCGCTCCCG GCCTCCTGGC GGGTGGCCGT TGGGCCCGTG TTCCCTGGG  
10 GCCTGGGGCT CCCTTCTCTC GCCCTTCTTG CTGGGCTCT GCTGCTGCTG GTGCTGTGGC CCCCCTACA CCGAGGAGCC  
CATGATGGGC ATGCCACAGA CGACAGGCGT BCBCCGBGBB GCCBTGBTG GGCBTGCCBC BGBCGBCBGG C GGC GCC GTG  
CCG CGT CTT GGT GGC GGC GG GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC GTT CGC GCC CGC GCG GGG CCC CTC  
CGG TCC CGG GTC GGG GCC CCC CGC GGC C GCC TCG GGG CTG GGG CGC TGG TGG CCG GG CCG CGC CTC CGC CTG  
CCG CTT CTG GCT GGG CCC CGG GCG CCC CCT CCC CTC TTG CTC GGG TCC CCG TG ACA GCG CGT CCT GTG TCT CCA  
15 GCA GCA TGG CCG GGC CAG CTG GGC CCC BCB GCG CGT CCT GTG TCT CCB GCB GCB TGG CCG GGC CBG CTG GGC  
CCC ACA GAG CAG TGC TGT TGT TGG GCA TCT TGC CTT CCC AGG G BCB GBG CB TGC TGT TGT TGG GCB TCT TGC CTT  
CCC BGG GCC CTT TTC TGG TGG GGT GGT GCT GTT GTT GGG CTT TCT TCT GTT CCC BCB GBG CBG TGC TGT TGT TGG  
GCB TCT TGC CTT CCC BGG GCC CTT TTC TGG TGG GGT GGT GCT GTT GTT GGG C TTT CTT CTG TTC CC TTT CCC CTG  
GGT CTT CC CTC CTG CTC TTT TTT C ATT TGC TCT CCT ATT ACT TTC TGT GTC CAT TTT TTC ATT AAC CGA GCT GT  
20 BTT TGC TCT CCT BTT BCT TTC TGT GTC CBT TTT TTC BTT BBC CGB GCT GT GCC TGT GTC TGT CCT CCT GCT TCG TTC  
CTC TCG TTC CTG CTT GGT GCC CTT GCC G GTC CTG CTC CTC CGG GCT GTG G GTC GTG GCC CTG GCT CCG GCT GGT  
GGG CTC CCC TGG CCT TCG CTG GCT GGC GGC GTG C GGG TCT TGC TCT GGG CCT GGC TGT GGC CGT GGT TGG GGG  
TCT TC GCT GCC TCC GTT TGG GTG GC TCT CTG AAT ATT GAC CTT CCT CCA TGG CGG TCC TGC TTG GAT TCT CCC  
GA TCT CTG BBT BTT GBC CTT CCT CCB TGG CGG TCC TGC TTG GBT TCT CCC GB GCC TTT CCT GGT TCT CTT GTT GTT  
25 TTT GGG GTT TGG CTT ACA GTA GAG TAG GGG ATT CCA TGG CAG GAG CCA TCT TCT TCA TGG ACT CC TTC AAG GAG  
ACC TTA GGT TTC TGA GGG ACT GCT AAC ACG CCA TCT GGA GC BCB GTB GBG TBG GGG BTT CCB TGG CBG GBG CCB  
TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB GGG BCT GCT BBC BCG CCB TCT GGB GC GTT GTT  
TTT GGG GTT TGG CTT GCC TTT CCT GGT TCT CTT BCB GTB GBG TBG GGG BTT CCB TGG CBG GBG CCB TCT TCT TCB  
TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB GGG BCT GCT BBC BCG CCB TCT GGB GC GCC TGT CTC TGT CCT  
30 CCT GCT TCG TTC CTC TCG TTC CTG CTT GGT GCT CTT GCC G GTC CTG CTC CTC CGG GCT GTG G GTC GTG GCC CTG  
GCT CCG GCT GGT GGG CTC CCC TGG CCT TCG CTT GCT GGC GGC GTG C CCC BGB BCG BGB CCC GGB CCG BCB GGC  
CGT GGT TGG GGG TCT TC GCT GCC TCC GTT TGG GTG GC GAT CTC TGA ATA TTGA CCT TCC ATG GCG GTC CTG CTT  
GGA GBT CTC TGB BTB TTGB CCT TCC BTG GCG GTC CTG CTT GGB TCT GGG GTG TCC TGG CCT TCG TGG TTC CTC TTC  
CTT CGT TTG CCG TCC GCG GGG GCC CCC GGG CCT GGC TGC GCT CCT GCC CCG CCT CTT TCC CGG GCT CTT GCG CTG  
35 GGG GGT GCT CC CGT GTG TTT GCG CCC TC CTC CTG GTC GCG CTT GTC GTT TTG GGG CCG GCT TTG CCC GCC TCC  
CGG CGC CTG GCC CGG CC TTC CTG GGC TGC GTG CGC GTT CTG TTC TTC TTC CTG GCT CTG GGG TGT CCT GGC CTT  
CGT GGT TCC TCT TCC TTC GTT TGC CGT CCG CGG GGG CCC CCG GGC CT GGC TGC GCT CCT GCC CCG CCT CTT TCC  
CGG GCT CTT GCG CTG GGG GGT GCT CCC GTG TGT TTG CGC CCT CCT GGT CGC GCT TGT CGT TTT GG GGC CGG  
CTT TGC CCG CCT CCC GGC GCC TGG CCC GGC CTT CCT GGG CTG CGT GCG CGT TCT GTT CTT CTT CCT GGC GCA GGA  
40 GAC AGG GCA GGG CGA TCA GGA GCA GCG TGA GCC AAA GGA GGA CCA TCG GGA ACG CAG CTG CCG AAC GCA GGA  
CAG AGG TGC C GC BGG BGB CBG GGC BGG GCG BTC BGG BGC BGC GTG BGC CBB BGG BGG BCC BTC GGG BBC GCB  
GCT CCG GBB CGC BGG BCB GBG GTG CC TCT GCC CTG TCC GCC GGC TCT TCG GTG GCT CGG CCC CGC TCC TTG TCT  
TGC CGC GGG TTG GTT CCT GGG CCT GGT TCT TGC GGG CGT TTC GGT CTG CTG GCT GGT CTG GGC CCG CGG TGC GGC  
GGG TGG CTT GCT GTT CTG CCT GGG CTC TCC CCT CTC CTC CTT TTC TCC CTT CCT CTG TCT TGC CTC CTT CCT CTG  
45 GGT CCT CTT GGC CTG GGC GCT CTT CCC CTC GGG CGG CTG CGG GCG CTC GTG CTG CCT GGT CCG CTC CCT GGG GGT  
GCT CCT TCC CTT TCC CCG CTC GTG GGG TTT GCG GGG CTG GGC TGC CCT GGG GGG TCT GGG CCT TTT GGG GTC GGC  
TGG CTG CTG CTT CGG GCC GCC TGG GCT TCC CTG TGC CCC TTT CCT CTG CTG GGT CCC CCT CCC GTT CCA AGC TGC  
ACC GCA CAG ACC GGC GCT ACA GGA CAG AGC CAG GCA AGC ACC CAT GGG GAT CCA GGC CCA GCT GTT CCB BGC  
TGC BCC GCB CBG BCC GGC GCT BCB GGB CBG BGC CBG GCB BGC BCC CBT GGG GBT CCB GGC CCB GCT G  
50 CTCAGTGGCC CCCAAAAGGA TGAGTAATAC ATGCGCCACG ATGATCATAT CCTTTTACT ATGAGGCCGT GTCTGTCTGT

TCTTTCCTTT GCTCTTGGTG TGCTTTTGTG GTGCCCTGCC TCTCTGCCCG TGCTGTGCTG GTCTTTCCTT TGCTCTTGGT  
GTGTCTTTGC TGTCCTTGC CTCTCTGCC CGTGTCTGTC GTGTCTTTCC TTGTCTTTG GTGTGTCTTT GCTGTGCCCT  
GCCTCTCTGC -GGGGGTGGCT TCTTGCCGCG TCTCTGGGCC GTCCCGTCCC TCGGCCCGCG GCCGCGCTCG GCTCCTCTCC  
CTCTGGCCCG GCTCGGGGCG GGGCGGGGCG GTGGCGGGG GCGCTGCCCG TGCGCGCGCG GCTGGCCCTG GCTGGCCGTC  
5 GGCTGCGCGC TGCTGGCTGC CTTGCTGCC GCGCCGGGGC CTGTCCGCT CTGCGGGGCG TGCTCTCTGG CTTGTCTTCC  
GGCTCTTCTG CTGGGGTGGG GCTGGGCGCG CGGCCCGGTG CTGGGGCTCC TCGGGGGGGG GGGCTCTTCC GGGCTGTCTC  
CCTCCGGGGC GGGGGTTTCT GGGCGTGGGG GTCTTGCTG GCTCCGGGC TCTGCTTGT CTTGCTTCC TTCTCTGGTC  
GGTTGTGGCT CGGGGCTCCG TGGGTCCCTG GCGCCCGTTT GTGTTTGTG TTTTCCCTG GCTCCCTGT GCCCTCTCC  
TCTCTTCT CTGCTTCTG CTCTCTTTG TGGGGCCCTC CTTGCTGTC TTGGTTTGG GCTTTTTC TTCTCTCTCT  
10 TTTTCGTGCG TGGGCTCC GCACGCTCT TGCCACCTCC TGCGCAGGGC AGCGCCTTG GGGCAGCGCC GCTCCCGGCG  
CGGCCAGCAG GGCAGCCAGC AGCGCGCAGC CGACGGCCAG CATGCTTCT CTTGGCTAC CACTCCATGG TCCCGCAGAG  
GCGGACAGGC GCBGCGCTC TTGCCBCTC CTGCGCBGG CBGCGCCTG GGGCCBGGC CGTCCCGG GCGGCCBGC  
GGGCBGCBG CBGCGCGCBG CCGBCGGCB GCBTGTCTC TCTCGGCTB CCBCTCCBTG GTCCCGCBG GCGGCBGCG  
C GCTGCCCGG GGGGTGTGCG CTTGGCGCT CCGTGTCTG TTCTGTGT CCGGTCCCG CTTGCTTGG GCTCTGGCC  
15 TTCTCTCT TCTCTTCT CTTTCCGCT CTTGGGGCT GCTTGGTGG GCGCTGTGCT CCGGGTCCCG GGGCTTCTGG  
CCCTTGGCGT TCATGGTGGC TAGGTGGGG GTTCBTGGTG GCTBGGTGG GC GGG GTG GGT BGG CCG TGT CTG GGGTT  
GGC CBT GTT GGT TGC CTCT TGG TGG TGC GCC GGG CCG TCT TGG CTT TCT TCT CCT TCG GGC CCT CGG GCC GGT  
GCT TGT GGGCT CCT CCC GGG CGG CCT CCC CGG GCG GGG GCT TCT TGGCG CTG GCG GGG GGG CCT CTTGCT CTG  
TGG CTG GGC GTT CCT TGG TGT TCT GGG TGCTG CGG GCG TGG TGG CCT CTG TGGGGG CCC GCG GCT GCB GGG  
20 GTTG CCT GTC TGC TTC GTCTT TGC GCT CCC GGG CCG CCGGG GTG GGT AGG CCG TGT CTG GGGGT GGC CAT GTT  
GGT TGC CCGG CCC GCG GCT GCA GGG G ACAGGGGCTG TAATCTTATC TGCAGGTGGC ATGCCAGTGA AATTAGATC  
ATCAAAATCC CACATCTGTG GATCTGTAAT ATTTGACATG TCTCTTCTG TTTAGCAAT GGTGTGATCT AACTGAAGCA  
CCGCCAGGB CBGGGCTGT BBTCTTCTG TGCBBGTGG BTGCCBGTG BBTBTBGTG BTCTBBBTCC CBCBTCTGTG  
GBTCTGTBBT BTTTGBCTG TCTCTTCTG TTTCBGCB TGGTTTGTG TBBCTGBBG BCCGGCCBG TGGCTCGGTG  
25 CTTCTGCCCC TGTTGTGCG GCGCTCGGT GGTGTGGCC CTGTGGTGT TCGTTTCCCC CTCTTCTCT TTGTTCGGGG  
GTTCTGTGG CGGGCTGCT GTCTGTTC GCCCTGTGCG GCGGGAAGCC TCTCTCTCT CCCCAGATC CCGACAGGC  
CGCAGGCAAG AACAGCGCA ACCAGGGCG GTCCGCACAG ACTTGAGGCG GGTGCAATG TGTACCTGC TCCAGAAGCG  
TCCGGTGGCC GCCGCGCC CTGTGGGCG GGBGCGCTCT CTCTCTCCC CBGTCCGCG BCBGGCCGB GGCBBGBCC  
BGGCBBCB GGGCGCTCC GCBGCBCTT GGBGGCGCT GCBTGTGCT BCCTGCTGGGCG GGBGCGCTCCG  
30 GTGGCCGCG CGCGTCCGT GCGCGCGCG CTTCTCTCT CTCCCGTGG CCGTGTGGG CGGGTCTGC CGTCTGTCT  
CCTTTCTTT TGCTGTCTT TCTTCCGTC TGTGCTT GTCTGTCT CCGTCTCT CCACTGCTT CTCCGGGGG  
CTTCCCGGC TTGGGTGGC CGGTGTCCG GGTCCGGCG GCGCGCGCG TCGGCTGCG GGTGGGTGG CCGGGCTCC  
GGGTCCGCG GCGCGCTGG CCTTGTGCT GCTTTTGTG TGTTCGTT TGGCTGTCC GGTGTGTT GTGTTTGT  
TGTCTTCT TGGGTGTGG CCTTGGGTT TTGGCTGTG GCCCTTGGG GCCTTGGCT CTGGCTGTC TGCTCTCC  
35 GTCTCTCC ACTGCTT CCTGGGGCT TCCCGGCTT CGGGTGGCG GTGTCCGGG CTCCGGCGCG GCGCGGCTT  
CGGTGCGGG TGGGTGGCG GGGCTGCCG GTCCGCGCG CGCTGGGC CTGTGTGCT TTTTGTG TTCCGTCTG  
GCTGTCCG TCTGTGTTG GGTGTTTTG TTTCTTCTT GGTGTGGGC TTGCGGTTT GGTGTGGC CTTTGGGG  
CTTGGCTTCT GGCTCCAT CCACATGATT GCTTAGATT GTGTGTATC TCTCAGGATT ATCACTGATT ACACATCCAA  
40 CCAAGTCCAG CAAAAGGAT GCCCTGAGG AAAGGGTTT CATCTTGAGG CAAATTTAG GACBTCCBC BTGTTGCTT  
BGBTTTGTG TGTBTCTCT BGGTTTCTB CTGTTTCTB BTCCBBCCG TGCCBGCBB BBGGTGGCC TGBGGCBGG  
GGTTTCCBT TTBGGCBGB TTTGBGGGGCTBBGT GBTCCBCTC BCTBCCBCT TGCCCBCCB BGBGTCTBC  
BCBTBCCG TGTBGGCBG TGCCBBBGG BCBTTTGGC BGGCTGGTG CBBGCTGB TTGGTTCCG BGGTGTBGT  
GGBGTGTTT GGGGBGGT CTBGTCCBC CCGGBGGCG TBTCCBTT CBBGCTBGG CGGTBBGCC CTBCTCTG  
TBCBCCBCC CCTCTGCBG CBGCTCTG TCGTGGCGC TGGGGCTCBG GGTCCGGC TAAGATGAT CACATCACTA  
45 CCAGTTGCC CACCACAGG GTCACCAA TGACCGTGA GGCAGTGC CAAAGGACAA TTTGCCAGG TGGTGCACG  
AACTGATTG GTTCCAGGT GTAGTGGAG ATGTTGGGG AGAGTCTGA GTCCACGGG AGGACGTTAT CCATTTGAA  
GCTAGGCGT AAAGCCCTAC TATCTGTACA CAACCCCT CTGACGAGA GTCTGTCTG GCGCCTGG GCTCAGGGT  
CTCTGTCTG TGGCGCTG GGTCTTCTT TTGTGGGCT TTGGTGGCT GTGGTGTG TCTGTGTG TGCTGCCCTG  
50 GGTCTGGGG TGTGGCTT GGGCGTCT CTGGCTCTC CTGTTGGG CCC GGTGCBTTG BCBGTGCTG  
CGCGTCCG TTBGGTGG GCGGCCAGC CCAGCCACT CACTGGGG CGGGTGGCA GCACGAACAG CACCAAGAG  
AAGGGGGCG GCCAGAAG CGACCCGCA GCCAGGATC AGTCTGCTG CGCGCGAGA TAATGGCAT CACCAAGCG  
CGGCCAGCG CACCGCGC ATCCGGCGG GTTCTGACC TGCAGCCCC GTCTCTTGG CATCTGGG CCCCAGAC  
TCTCTCTT GCGCCCTT CTGGGCGAG GACGGGTG BCBTTBGB TGTGGCGCG GTCCGTTB BGTGGGGC  
GCCAGCCAG CACTCCACT TGGGGCGG TGGCAGCAC GAACAGCAC CAGAGGAAG GGGCGGCC AGAAGGGCAG

CCCCAGGCC AGGATCAGGT CTGCTGCGGC CGAGATAAT GGCATTCACC ACGCGGCGGC CCAGCGCACG CCGCGCATCC  
 GGCCCGGGTT CTGACCTGCA GCGCCCTCT CTTGGCATT CTTGGGCCCC AGTACTCCT CTCCTGCCC CCCTTGCTGG  
 GGCAGGACG GCCGTGTGT CBGTGGTCT GCCGTTTGB GGTBTGGCG TCCBCCBBT CCCTTTTCTC CTGTGTTTCC  
 GTTCTCTTG CCGTCTGTGG TT-3' (SEQ. ID NO:2409)

# 5 **Human Enzyme-related Antisense Polynucleotide**

5'-CTT GCT CCT GGG GGC CTC CTG GTC CCT CTG GCT G TT CCC GGC CCT GGB CTG GGG CBG GGG CCG CGT BGG CGC  
 GGC TCG CCB GGB CGG GCB GCG CCB GCB GCB GGC TCB GCB TCC TGG CCB CGG BBT TCC GGT GTG CGG GGC  
 CTG GTG CC CCT GGG CCT CGG GTG CTG CCT GT GCG CTG CCT TCT TCT CCT GG GTC CTC GCC GGG GCC CTT GCT GCC  
 CTG GCT GT GCC CTG GGG GTC TGG GTT CGG CTG T CCC CBG CBG GBC CBG TCC CBT CCB CBG CGT GTG BTG BGT BGC  
 10 CBT TCT CCT GCB GCC GBG GGG CGC GGG CGB GCB TCG C TTT GGG CTT TTC TCC TTT GGT T TGB GCG CCB GGB CCG  
 CGC BCB GCB GCB GGG CGC GGG CGB GCB TCG CBG CCG CCG GCB GGG GGGCTCCCGC CGCGBBGGT TBTGGGCTCC  
 CBGBBCCBC CGCBCCGCGC GGBCGTTTBC BTTCGCCBCG CBGTGCGCGG CCGBCBTGBC GBBGTTGGGC GCBBTBGGG  
 TGGCGCCGB GBBGTGGCCT CCGCGCBGCT GCBGGGBCB CBTGBBGGG CBGCGTGGG GCCGCGCTCG CCGGCCCCC  
 BCBTCTCCG BGGCCBGGC GGTGCCCCC BGCBCBGG CCGCBGGBC BCBGGCBGG BGCBCGCBG GTCGGCGGCC  
 15 GBBGGTCTG GTGGGGCTGG GGCTCCGGG TCTCTGCCCT TCCGTCTGG TGGGGCTGG GCTCCGGG TCTCTGCCCT  
 TCCGTGCCG GTGGGGCCG GCTCGCCGG CCCCCCTGC CCGGTGGGT CCGCGCGCG CCGGCTGC CCGCCCTCG  
 TGGGTCTGC TGGCCGGGT CCGGTCCCG GGTGGGGCG CBGTGCGCG GCCBGGGTC CCCTCCCBT CTGCTCTGBC  
 CTGCTGGBCT CTGGBTCTG BGBTBCGCC TGTBGGGGC GBBGTGGGG CTGCTCTCC GGCCTCCGT GBTCTCCCT  
 20 GCCTCBGCCC CBGTGGGTG GBGBBGGCC BGCBBGGCB GBBGTGGGT CBTCTTCTT GGTGGGGCT GCTCTCCCG  
 CCTCCGTGTG TTGCTGGGTG TTTTCCGTC TCTGGTCTG CTTCGGGGT CGT CCGGGGCTGC BGCBBCTCB TCBGCTCTG  
 CCTGGBGTG CTCBGCCTG GCCTGCBGG CCBCCBGGG BBTGGCBGB BGGBTGGCB GGGTCTCBT GGCTGGGGT  
 BCBGTCTC TBGCTBGGCB GGGTGBCCB BGGGGG GGG TCC TCB TGG CTG GGG GCC TGG GCC TGC BGG GCC GCT  
 CTT GCC TGG BGT GGC TC GCC CBG BGT CTT CCC TGG T CGTGCBBTC TGCTCCGGG CTGCBGCB CBTCTCBGCTC  
 25 TTGCTGGBGT GCTCBGCTGG GCCTGCBGG CCBCCBGGG BTGGCBGCB BGGBTGGCB GGGTCTCBT GGCTGGGGT  
 TGGGGTCCCT GGBGGGGG GBGCBGGGG TCCTCBTGG TGGGGTCCCT CTCTCCGTC CT CGG TTT CCT TTG CGG  
 TC TTG GCC CGG GCT CCG GGT G CCC GCC CGC CCG GCC GCC GC CCC GCC GGG CTG TCC CCG CCC CGC CCC GGC  
 CCG GGG CGC GGG GG CGG CCC TCC CGC CCC TCT GG GCC GGC CGG GGC GTC GG CCG CTC GCG CCT GGG GTT CCC  
 TCT CCT CCC CCT GTG C GCC TGC CTC TTG CTC TTCTG GTC CGC TGC CTT CTC CC CTC TCC TCG GCC GTT GCC TGT  
 30 GC TGT CCG TCC TGT CGC CCT TCC GTG GTG C TGT TGT CTC TTC TGC CCT C GGT GTG CTG GTG GTG GTG GTG  
 CCT CTG CCC GTG CTC GCCCTG CCT GGG CTG GCC TCT TCG GGT GTG GCT TTG GGG CTC TCT TGG TTG CCC TTT CTT  
 CTC GTG GTG CCT CTC CTC CCT GGC TTG GTC GT TGT CTG GGG TGG TGC TCC TCT CCC TTT CCG TGG CCG TTT  
 GT CCT GTT TTC TGT CTT CCT CT TTC CTC CTG TTT CTC CGT TTG GCT TGC TGC TTG CCG GGC TGT CTC C CTT GCC  
 CCT GTG GGC TTT CCC TGG TCC GGT CTT CTC CTT GGG GGT C GCC CTT CTT GGT GGG CTGGCT CGT CTG TCT TTT TCC  
 35 TTC C TGG GGG TGG CCG TTG TGG GCG GTG TGG TCC GCC T TGC CTC TGC TGG TCT TTC -CTCGGTBGC GCGCTCBBC  
 TCGGGTGGG CGGTGTGGB CGCGCGCBG CCGGBBGGC CCGCGCGCC GGBTCBCCGT CBGGGBBGG TBGGCTGCB  
 GCBGGCTCC CBGGGGGTG BCBGCBGCC GTBGBGCTB CTCGTCTTC BTGGTBCCGT CCGGTGTGGT GCBGCGGCTG  
 TGTGTBBGG CBGCTGGG CCGCTCTGCT GCTCTCTT CCGCTCTGCT CTCA TGG TA CCGTCGGTGT GGTGGCTCG  
 GGTGGGCCG TGGTGGGGC CGCGGCTCG CTGGCTCCG GCTCTCTT CCGGCTCCGT CCGCCCGGG GCCTTGGTCT  
 40 CCCTCGTCT TCBTGTBCC G BCCGGCGBG CCGCCBGGT GGBCTGGBG TGGGTCTCT CCGGCTCCGT CCGCCCGGG GCCTTGGTCT  
 CGCTGBGCT BCGGCTBBG BCTGTGTTT CTGGBGCTCC TTGGCBGGC BCBBCBGB GBBGBBBBT CBTGBGCB  
 TBBTCCBT TGBBBBBBB GGBTCBBBB CCTCCGTT CCGGTTCGCC TGGCGCGCG TCGGGTTC TCGTGGGTT  
 CTCGCCCG TCTCCGTC TGTGCTTT GTGGGCTT TGTCTTTT GCTGTCTTT TCTGCTTG CGTCTTTT  
 45 TTTCTTTG CTCGGTTGT GGTCCGCTG TCCTTTGCC TGTGTGTT TGTGCCCC TGCTGCCGT TGCTGCGG CCGCTGCGG  
 GTTCTCTG GGTCTTCC CCGGTTCT CCGTCTGT CTTTGTGG CTCTGTCT TTTTGGCTG TCTTTTCTG  
 CTTGGGCTT TTTCTTCT TTGTGCTCG TTGTGGTCC GCTGGTCTT TGCCCTGTG GTTCTGCTG GBBGCTGCTB  
 CTGCBGATT CBGGBGGBB BCCCTGCTB CTCBCCGCT TCBGCTCTG BGCBCBGB BBBGBGCBG BGGGGGBGB  
 GBBGBGCB CBTCTCCCB GBBGGCTGC CTBGCBBT GCTGTGTTT CTTTCCBGT TTGGGTTTB TBBCTCCCB  
 BGGCBGBG BGGGCBGG CGTTTTCT TCTCGTGT TTTCTTTC TGCAAGTGG TGGGGTGG GGTGGGGTGG  
 50 CTTCTTGT CTTGGGGGT TCTCTTGT CTGGGCTTT CTCCTTTT CTTCTCTG TGTGTTTCT TGTGTTCT CTTCTCTG  
 CTGCTCTGT GTCTTGCC TGGCCCTCT CCTCTCTG TCTCTGTC CTGTGTTCC CCGTCTTC CTCTCTGAC  
 CTCTTTTCC TCCGCTGGT GGGGCCCTG CTGTCTCTG CTCCTGGCT TGGGGTTCT TGTGTGTC TCTCTCT  
 GTTGGCTGC TTTCTCTT TTTGTCTT CTGGGTGCC CTCTCTCT TCTTGGTCC TTGGTCTG GGTGGG

GCGTCTTGGG GTGCBGGGCC CBTCTGCTG CGCTGGGCG CTGCTGTGCG TCCGTCTGCT GGGGGGCCGG GGTGGCTGGG  
 CCTGTCTGC CGACGACCC CGGGCCGACC CGAGGCTCGG GGGGCTGTGT TCTGGCGCTG GTGGGCTTGG GCCCTCTGCG  
 GGGCTGGGTT TCCTGCTGCG CCTGGGCGCT GGCCTCTTGG GTGCGGGGGC CGGGGGGCCG GGGGGCCGCT GTTCGTGGGC  
 5 CTGGGGGTGC CTGTGGCTGC CGGTTGCCCC GGTGGGTGGC GCCGTCTGCG TGCCGGTCTG TGGCTGGGTC CCCCCGCCCG  
 TTCTCTGGGG TCCGCTGGG GTGCTCCGGT TCCTCGTGCC GCTGCTGCCT TGTCTTCCG GCCGTGGCGG CGTGGTGGTC  
 CGCCCCCCT GGCCTTCTGC TCGGGGTCTG GCTGGTTGCC GGTGCCCTTG GCGGCGGTCT TCTTCTGGT GGCTCTGGGC  
 CCGGCCGGTC TCGGGCGTCT CGTGTTCGCT CTGTGTGTGT TCCGGCCGCT CTTCTCTTT CCGCCGCCGC CGTCCCGGC  
 CCGCTCTGCG CCCTGGCCCC GCTCTCTCT GGCCTGTGTC TCGGGCGGCG GCCTTGGCGC TCCGTTTGGG GCTGCTCTG  
 GCGCTTCCGG CCCTCGGCTT GGGCGCTCTC TTCCGCTGT GCTGGTGGCC CTCGTGGGCC CCTCTGGCC TCCGGTGTCC  
 10 TGTGGTCCCC CGGCTGGTGG CCGGGCCGGT TGGGCGGGCG TGGGCGCCGG CGGCTCTCC GGGCTGCCCT TCTCCGCCGG  
 GGGTCCCGCG CTCCTGCTGT TCCCTGGGCT CTCTGCGCT TCTCTGGGT GGGTGTGGG TGCCGGGGTC TCCGGGCTTG  
 CCCC CGCTG CTGGGCGTTC TCGGTCTTG GGGTGTCTG TGGCCCCGCT CGTGTGCGCC TCCGTGCGCC GTGCGCGGCC  
 TCGTCCCTC CTGGGTGCGC GCGGGGCTGG TCCTGGCGTT TTGCTCTTC CTGGGCGTCT TGGGTGCBG GGCCCBTCCT  
 GCTGCGCTG GCGCTGCTG TCGTCCGTC TGCTGGGGG CCGGGGTGGC TGGGCCCTGC TTGCCGACG ACCCCGGGCC  
 15 GACCCGAGGC TCGGGGGGCT GTGTTCTGCG GCTGGTGGG TTGGGCCCT CTGGGGGCTG GGTTCCTGCG TGCGCTGGG  
 CGCTGGGCTC TTGGGGTGGC GGGCCGGGGG GCGGGGGGCG CGCTGTTCGT GGGCTGGGG GTGCTGTGG CTGCGGTTG  
 CCCC GTGG TGGCGCCGTC CTGCTGCCGG TCGTTGGCTG GGTCCCCCG CCCGTTTCTT GGGTCCCGG TGGGTGCTC  
 CGGTCTCTG TGCCGCTGCT GCCTTGTCTT TCCGGCCGCG GCGGCGTGGT GGTCCGCCCC CCTGGCCTT CTGCTCGGGG  
 TCTGGCTGGT TGCCGGTGCC CTGGGCGCG GTCTTCTTC TGGTGGCTCT GGGCCCGGCC GGTCTCGGG GTCTCGTGT  
 20 CGCTCTTGTG CTGTTCGGC CGCTCTTCC TCTTCCGCC CCGCCGCTCC CCGCCGCTC GTGCGCTTG CCGGCCCTCC  
 TCCTGGCCCG TGCTCGGGC GCGGCCCTG GCGTCCGTT TGGGCTGCC TCTGGCGCTT CCGGCCCTCG GCCTGGGCGC  
 TCTCTCCG CTGTGCTGGT GGCCTCGTG GGCCTCTCT GGCCTCCGT GTCTGTGGT CCCCCGGTG GTGGCCGGG  
 CGGTGGGCG GCGGTGGGCG CCGGCGGTC CTCCGGGCTG CCCTCTTCC CCGGGGGTCC CCGCTCTG CTGTTCCTG  
 GGTCTTCTG CCTCTCTCT GGGTGGGTG TGGGTGCCGG GGTCTCCGG CTGGCCCCG GCTGCTGGG GTTCTGCGGT  
 25 CTGGGGTGG TCTGTGGCC CGCTCGTGC GCCCTCCGTC GCCGTCGCC GGCCTCGTCC CCTCTGGGT GCGCGGCGGG  
 CTGGTCTGG CGTTTGTGCT CTTCCTGG CTGCCCBGT TTTGTBCTC CBCBTGCCGT GGGGBGGBCB BTGGCTGCCT  
 CCCCCGGTT TCTGTGCTT GTGTCTTCT TCCGCTCTC CTCTTCTCC GTCTCTTTT TGCTCTTTT GGTTCTTGT  
 GTTCTCTGCG TGGTGGTGG CCGCTTGTG GTTCTCTC TCTCTCTG GTCTCCGCT TCTGCTCTG CTTTCTCTG  
 TCTGTGCGC GCGTCTCTC CTCCGGGCTC CTCTGCCCT GTGCTGTTG CCTCGGGTGG TCGGGGTCCC GGTGCTCCC  
 30 CCGCGGGCCG GCTGGTGGC TGGGCTGTC TGGTGGGGT TGGGCGCGCT GGGTGGGGG TGTGGTGGG TCTTCTGTG  
 CCTGTGGGG TGTGGTGTG TCTGTGGGCG TGTGCTGGT CTGGGGCTT CCTCCCTGT GCTGGGTGCG GCCTCCCCG  
 CCCCCTCTG GCGCGGTGGC CTGGCTCCTT TGGGCGGCT CTGGCTCTT CCTGTCTT CTTCGCTCG TGGCTGCTG  
 GCTGC-3' (SEQ. ID NO:2410)

### Human Factor Related Anti-sense Oligonucleotide

35 5'-CCT CCT TCC TGG TCT GTC TGC CBG BCB BBT TTG GBB BGT CBG TTT TGG BBC CBT GTT TCC CBG TCT CTG BGC  
 TGT GGC GCC CTG CTG TTT CTG CT TCC CTT GGT GGG TTG GGC C GCT GGT TGT TCT GGG GTT C TTG CTG CCC  
 CTT CTG TCC C TGT TTG CTG GTG TCT GCG C 5'- CCC CBB CBG BBG BBG CBG BCB BBT TTG GGB BGT GBB CBG TTT TGG  
 BBC CBT GTT TCC TGT GCG CTC GGC CTG GTC CCG G GGG TCT CCT CTT GTT GTT GC TTG CGC CTC CTG CTG GGG GT  
 40 CC CTC TGT TCT TGT TTT GGG GGC GGG CCC GGC CGT TGT CTT G GTT TGG GGG TTT CCG TTG GGG TTC TCC TGG  
 CCC GGG CCT TGC CC GGC CGT GGT CCC GGC TTC GTTCTT GTC TCC GTC TCG GCT CTT CTG GGG CCT TGC GCT GTC  
 TTT GGT G 5'-GCB CCG TCC BGT GBT GGT GCG GTB CTT GTC GCT GCB GCG CTC GGC CTG GTC CCG GBB GGC GCG CGG  
 GCC GGG GGC TGC TGG G GGT TGG CCC GGG GTG CCC C GCC GCT GGG TGC CCT CGT CCT CTG CGG TC GTG TCT CCT  
 GGC TCT GGT TCC CC GCT GCG CCC GTT GTC CTC TGG GGT GGC CTT C GCT CCC GGG TCT GGT TCT TGT GT TGG GGG  
 45 TCC CTT TTT GGG CCT GTT GT GGC GTG GCT TGT GTG TTC GGT TTC TGC CCT GTC CTC CGG CGT CCC CGG BGC CTC  
 CCC GGG GCB GGB TGB CTT TTG BGG GGG BCB CBG BTG TCT GGG CBT TGC CBG GTC CTG GGB BCB GBB CCC CGB GCB  
 GGB CCB GGB GTG CGG GCB GCG CGG GCC GGG GGC TGC TGG GBB CCB TBG CGB GGC TGB G CCT CTT TTC TGT TTT  
 TCC C CTC TGC CTT TGT TTG GGT TCG CTT CCT TTC TGC TTC TTC C CTG TGT CTC CTG TCT CCG CTT TTT TCT TC GTC  
 TTT GTT GTT TTC TCT TCC TTG CTG BGC BBG BTB TCT BGB TTC TGG GGT GGT CTC GBT TTT BBBB GCT TGB GBB GCT  
 GCB BBC BTT BTC CBB BGT BTB TTT GBG GCT CCB BGG BTC BCG BCC BTC TTC CCB GGC BTT TTB BGT TGC TGT CGT  
 50 BBG TGB GBG CTG BGB GBB BCT GTG BBG CBB TCB TGB CTT CBB GBG TTC TTT TCB CCC GTT CTT GGC TTC TTC TGT  
 C CGT TGG CTT CTC GTT GTC CC TGT GGG CTT CTC GTT GTC CC CCC TTC GGG GGC TGG TGG GGC CGT CCT TGC CTG  
 CTG G GTT CTT GGC TTC TTC TGT CCG T TGG CTT CTC GTT GTC CC TGT GGG CTT CTC GTT GTC CC CCC TTC GGG

GGC TGG TGG GGC CGT CCT TGC CTG CTG G TTT TCT CTT TCG CTT TCT TTT CGT CTC CTG TTC CTC CTT TT TTG CTG  
TTT TTT CTC CTT CTT CTC TCC TTT CTT TTC TTT TCT CTT TCG CTT TCT TTT CGT CTC CTG TTC CTC CTT TT TTG CTG  
TTT TTT CTC CTT CTT CTC TCC TTT CTT TTC CTC TGT CTT GTT CTG GTC CTT CGT GGG GCT CTG TGT CGC GTG G GTG  
5 CGG CCG TGG CC GGC GGB CCB GGB GTT GGB GCB GGB GCB GGB CGG GCB GGC GGC TCB TGT TTG GBT CGG CBG GGB  
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BCC CBT TBB TBG GTG TCG B TCCCTGTTTC CCCCCTTTTCG TTCTGCGTTT GCCTTTGGCG TTTTGTGTTT GTTTTCTCTC  
TCCGTCTTTC TTCTCCCT GTGGGBBTTT CTGTGGGGBT GGCBTBCBCG TBGGCBGCTC CBBGBGCTBG CBBBCTCBBB  
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AAACTCAAAT GCAGAAGCATC CTCATGGCTC TGAACG GGGGGTGGCT TCCTGCCGCG TCCTGGGCC GTCCCGTCCC  
10 TCGGCCCCCG GCCGCGCTCG GCTCTCTCC CTCTGGCCCG GCTCGGGCG GGGCGGGCG GTGGGCGGGC GGCCTGCC  
TGGCGCGCGC GCTGGCCCT GCTGGCGTC GGCTGCGCG TGCTGGCTGC CTGTGGCC CGGCCGGGCT GTGCGGCTC  
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TCCTGCTGT CTTGCTTCC TTCTGTGTC GGTGTGGCT CGGGCTCCG TGGGTCCCTG CGGCCGTTT GTGTTTTGTC  
15 TTTTCCCTG GCGTCCCTGT GCGCTCTCC TCCTCTCT CTGCTTCTG CTCTCTTTG TGGGGCCCTC CTGCTGCTC  
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CCTCGGTAC CACTCCATGG TCCGACAG GCGGACAGG GCBGCGCTC TTGCCBCCTC CTGCCBGGG CBGCGCCTG  
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20 CCBCTCCBTG GTCCCGCBGB GCGGBCBGG C GGGGTGGBB GGTGGBGT BTGTCTTBT GCBTGCBCT CTBBGTCTT  
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25 CTCCCTCCB GTCCTTCTG TCCGCTGCC GCBCCCTTC BTCCBGBGG CTGTTGGCT CCBCCBGGG CBTGTTBGG  
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30 TGGCAGGAGT GCATCCCAT GTCAACTCT GTGTCTGTG CATAGCTCT TGTGTGTTT GAGATTCCA TCCCGGCTTC  
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GCGCBGGGG CBGTGCBBT GBGBGTBGB GCGGGCGTG CCGCGGBGC CTCTBTGGT CCGTGGGBB GGCTGTGGB  
35 GGGGTGTGG TGTCGGCTG GCGGTCTTT CGGTGTTC TTCTCTGGT TGGCTGCTG CTCGTCTGCT CGCTCCGCTC  
CGGGTCTGT CTCGCTCTG CCGCCCTTC TTCTGTCTG TGTTCTCTC TTCTTGCT CT GBTGTTGTT BCCBBGCBT  
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BGBGCTGB BBTBGBBGG CTGCCBGBGB CCBGCGCBG TTGGGTCTBT GTTTCBGB BGBTGGGTG  
40 TCCGGTGGT TTTGCTGT GTGCTCTG GTCTCTG TTC CTCCGGTG TTCTTCTG GCTCTGTCC TTCTCTTG  
CCCTTGGCC CTGGBGBGG BBGCTCTGG GCBGGGCT GCGGGGCTG CTCTCTGCT GCTCTGTCC TTCTCTTG  
GCBCTGTGCC BCBGBGBG CTGCBGGGC BTGCTCTB TGGGCTCTG GGTGGCBGT CCBGCCBTG GTCTGGGTG  
GGCTGGGCTG CBGGCTCCG GCGTCCBGGCTGGTCTG GGGGCTGG CTGCBGGCT CGGGCGGGG GGTGCGGGT  
GCGTGTGGG GGCTGCCCG CAGGCCCTG GGTCCBGG TGGTCTGG GGTGGGCTG CBGGCTCCG GCGGGGGGT  
GCGGGCTG TGCTGGGGG TGCCCGCAG GCGCTG GCBCCGCTG GBGCGCTGG GCGCCCTGT CTCTTGGG  
45 BCGGCTCT CCGCBGCTC BCGTCCCG BTCTGCTT CBTGTCTBT GGTGTCTT CCBGGGBB GBGGGGCTG  
TCCTGTCT TCTGTCTG TGCTBTGT GTCTTCTC CCCTGGGGC CCGTGTCT CTGGGGCT CTCTCTCTG  
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50 TGTCGCTGB GGBGCGTCT GCTGGCGTG GTCTGTCTG CTGTGTGTG CTCTGTGT CTCTTCCG CTGGGGCCCC  
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GGGCBTCT CTGCBGBB TGCTCBGG GCTCCGCBG TTCTCTCT BTCTGTGCTG GCTGTCCB TCGGBCCBT



BBTTCBGBTC BTCBTGGCT CCTBTTCCTT CTGCBBCBG CTGBGTGGG BCBBGBBBB BGBCTGCCBB GGCCBCBGG  
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 5 CCTCTCTTG GCTGGTCCCT CGTGTCTCTT GGGCCCCG TCCCGCTGCT CGGCCTCCGT GTTCTTTGGC CTCTTGCTCC  
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 10 GCTCGGGGCT GTTCGTCCCC CTGCGGCTC TGTGGCTCC GGGGCTCTC GTTTCGCTG CTTCGGGTGT CCTTCTCGGC  
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 15 CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC CCT GCC GTG TTG TCT GTG GGT GTC GTT TCG CTC  
 TTG TTG CCC TGG GCC CTT CCC TGC TGG GGG GGA GTT TCA TCT TGG GTT TCB TCT TGG CTT TBT CCTCT CCC CTT  
 GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC CCT GCC GTG TTG TCT GTG GGT GTC GTT TCG  
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 CCGTGTGTC BTGGGTGCTG CCGTTTGBG GTBTGGCGCT CCBCCBBTTC CCTTTCTCC TTGTTTCCG TTCTCTTG  
 CGTCTGTGGT T-3' (SEQ. ID NO:2411)

## 20 Human Adenosine A<sub>1</sub> Receptor Anti-sense Oligonucleotide Fragments

5'-GAT GGA GGG CGG CAT GGC GGG-3' (FRAG. NO: 1657) (SEQ ID NO:1670)  
 5'-G CGG GTC GCC GG-3' (FRAG. NO: 1658) (SEQ ID NO:1671)  
 5'-GGC GGG CBC BGG C-3' (FRAG. NO: 1659) (SEQ ID NO:1672)  
 5'-GGC GGG CBC-3' (FRAG. NO: 1660) (SEQ ID NO:1673)  
 25 5'-GC GGC CTG G-3' (FRAG. NO: 1661) (SEQ ID NO:1674)  
 5'-GGB GGG CGG C-3' (FRAG. NO: 1662) (SEQ ID NO:1675)  
 5'-GBT GGB GGG-3' (FRAG. NO: 1663) (SEQ ID NO:1676)  
 5'-GG CTG GGC-3' (FRAG. NO: 1664) (SEQ ID NO:1677)  
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG.1) (SEQ. ID NO: 11)  
 30 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 2) (SEQ. ID NO: 12)  
 5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 3) (SEQ. ID NO: 13)  
 5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 4) (SEQ. ID NO: 14)  
 5'-C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 5) (SEQ. ID NO: 15)  
 5'-CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 6) (SEQ. ID NO: 16)  
 35 5'-TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 7) (SEQ. ID NO: 17)  
 5'-G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 8) (SEQ. ID NO: 18)  
 5'-GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 9) (SEQ. ID NO: 19)  
 5'-AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 10) (SEQ. ID NO: 20)  
 40 5'-A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 11) (SEQ. ID NO: 21)  
 5'-AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 12) (SEQ. ID NO: 22)  
 5'-GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 13) (SEQ. ID NO: 23)  
 5'-C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 14) (SEQ. ID NO: 24)  
 5'-TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 15) (SEQ. ID NO: 25)  
 45 5'-GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 16) (SEQ. ID NO: 26)  
 5'-A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 17) (SEQ. ID NO: 27)  
 5'-GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 18) (SEQ. ID NO: 28)  
 5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 19) (SEQ. ID NO: 29)  
 5'-T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 20) (SEQ. ID NO: 30)  
 5'-GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 21) (SEQ. ID NO: 31)  
 50 5'-GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 22) (SEQ. ID NO: 32)  
 5'-A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 23) (SEQ. ID NO: 33)  
 5'-GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 24) (SEQ. ID NO: 34)  
 5'-GG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 25) (SEQ. ID NO: 35)  
 5'-G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 26) (SEQ. ID NO: 36)  
 55 5'-CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 27) (SEQ. ID NO: 37)  
 5'-GG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 28) (SEQ. ID NO: 38)  
 5'-G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 29) (SEQ. ID NO: 39)  
 5'-CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 30) (SEQ. ID NO: 40)

- 5'-AT GGC GGG CAC AGG CTG GGC-3' (FRAG 31) (SEQ. ID NO: 41)  
5'-T GGC GGG CAC AGG CTG GGC-3' (FRAG 32) (SEQ. ID NO: 42)  
5'-GGC GGG CAC AGG CTG GGC-3' (FRAG 33) (SEQ. ID NO: 43)  
5'-GC GGG CAC AGG CTG GGC-3' (FRAG 34) (SEQ. ID NO: 44)  
5 5'-C GGG CAC AGG CTG GGC-3' (FRAG 35) (SEQ. ID NO: 45)  
5'-GGG CAC AGG CTG GGC-3' (FRAG 36) (SEQ. ID NO: 46)  
5'-GG CAC AGG CTG GGC-3' (FRAG 37) (SEQ. ID NO: 47)  
5'-G CAC AGG CTG GGC-3' (FRAG 38) (SEQ. ID NO: 48)  
5'-CAC AGG CTG GGC-3' (FRAG 39) (SEQ. ID NO: 49)  
10 5'-AC AGG CTG GGC-3' (FRAG 40) (SEQ. ID NO: 50)  
5'-C AGG CTG GGC-3' (FRAG 41) (SEQ. ID NO: 51)  
5'-AGG CTG GGC-3' (FRAG 42) (SEQ. ID NO: 52)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 43) (SEQ. ID NO: 53)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 44) (SEQ. ID NO: 54)  
15 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 45) (SEQ. ID NO: 55)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 46) (SEQ. ID NO: 56)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 47) (SEQ. ID NO: 57)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 48) (SEQ. ID NO: 58)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 49) (SEQ. ID NO: 59)  
20 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 50) (SEQ. ID NO: 60)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 51) (SEQ. ID NO: 61)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 52) (SEQ. ID NO: 62)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 53) (SEQ. ID NO: 63)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 54) (SEQ. ID NO: 64)  
25 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 55) (SEQ. ID NO: 65)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 56) (SEQ. ID NO: 66)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 57) (SEQ. ID NO: 67)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 58) (SEQ. ID NO: 68)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 59) (SEQ. ID NO: 69)  
30 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 60) (SEQ. ID NO: 70)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 61) (SEQ. ID NO: 71)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 62) (SEQ. ID NO: 72)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 63) (SEQ. ID NO: 73)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 64) (SEQ. ID NO: 74)  
35 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 65) (SEQ. ID NO: 75)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 66) (SEQ. ID NO: 76)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 67) (SEQ. ID NO: 77)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 68) (SEQ. ID NO: 78)  
5'-GGC GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 69) (SEQ. ID NO: 79)  
40 5'-GGC GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 70) (SEQ. ID NO: 80)  
5'-GGC GGC CTG GAA AGC TGA GAT GG -3' (FRAG 71) (SEQ. ID NO: 81)  
5'-GGC GGC CTG GAA AGC TGA GAT G -3' (FRAG 72) (SEQ. ID NO: 82)  
5'-GGC GGC CTG GAA AGC TGA GAT -3' (FRAG 73) (SEQ. ID NO: 83)  
5'-GGC GGC CTG GAA AGC TGA GA-3' (FRAG 74) (SEQ. ID NO: 84)  
45 5'-GGC GGC CTG GAA AGC TGA G-3' (FRAG 75) (SEQ. ID NO: 85)  
5'-GGC GGC CTG GAA AGC TGA-3' (FRAG 76) (SEQ. ID NO: 86)  
5'-GGC GGC CTG GAA AGC TG-3' (FRAG 77) (SEQ. ID NO: 87)  
5'-GGC GGC CTG GAA AGC T-3' (FRAG 78) (SEQ. ID NO: 88)  
5'-GGC GGC CTG GAA AGC-3' (FRAG 79) (SEQ. ID NO: 89)  
50 5'-GGC GGC CTG GAA AG-3' (FRAG 80) (SEQ. ID NO: 90)  
5'-GGC GGC CTG GAA A-3' (FRAG 81) (SEQ. ID NO: 91)  
5'-GGC GGC CTG GAA-3' (FRAG 82) (SEQ. ID NO: 92)  
5'-GGC GGC CTG GA-3' (FRAG 83) (SEQ. ID NO: 93)  
5'-GGC GGC CTG G-3' (FRAG 84) (SEQ. ID NO: 94)  
55 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 85) (SEQ. ID NO: 95)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 86) (SEQ. ID NO: 96)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 87) (SEQ. ID NO: 97)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 88) (SEQ. ID NO: 98)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 89) (SEQ. ID NO: 99)  
60 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 90) (SEQ. ID NO: 100)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 91) (SEQ. ID NO: 101)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 92) (SEQ. ID NO: 102)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 93) (SEQ. ID NO: 103)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 94) (SEQ. ID NO: 104)

- 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 95) (SEQ. ID NO: 105)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 96) (SEQ. ID NO: 106)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 97) (SEQ. ID NO: 107)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 98) (SEQ. ID NO: 108)  
5 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 99) (SEQ. ID NO: 109)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 100) (SEQ. ID NO: 110)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 101) (SEQ. ID NO: 111)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 102) (SEQ. ID NO: 112)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 103) (SEQ. ID NO: 113)  
10 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 104) (SEQ. ID NO: 114)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 105) (SEQ. ID NO: 115)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 106) (SEQ. ID NO: 116)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 107) (SEQ. ID NO: 117)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 108) (SEQ. ID NO: 118)  
15 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 109) (SEQ. ID NO: 119)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 110) (SEQ. ID NO: 120)  
5'-GC GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 111) (SEQ. ID NO: 121)  
5'-GC GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 112) (SEQ. ID NO: 122)  
5'-GC GGC CTG GAA AGC TGA GAT GG -3' (FRAG 113) (SEQ. ID NO: 123)  
20 5'-GC GGC CTG GAA AGC TGA GAT G -3' (FRAG 114) (SEQ. ID NO: 124)  
5'-GC GGC CTG GAA AGC TGA GAT -3' (FRAG 115) (SEQ. ID NO: 125)  
5'-GC GGC CTG GAA AGC TGA GA-3' (FRAG 116) (SEQ. ID NO: 126)  
5'-GC GGC CTG GAA AGC TGA G-3' (FRAG 117) (SEQ. ID NO: 127)  
5'-GC GGC CTG GAA AGC TGA-3' (FRAG 118) (SEQ. ID NO: 128)  
25 5'-GC GGC CTG GAA AGC TG-3' (FRAG 119) (SEQ. ID NO: 129)  
5'-GC GGC CTG GAA AGC T-3' (FRAG 120) (SEQ. ID NO: 130)  
5'-GC GGC CTG GAA AGC-3' (FRAG 121) (SEQ. ID NO: 131)  
5'-GC GGC CTG GAA AG-3' (FRAG 122) (SEQ. ID NO: 132)  
5'-GC GGC CTG GAA A-3' (FRAG 123) (SEQ. ID NO: 133)  
30 5'-GC GGC CTG GAA-3' (FRAG 124) (SEQ. ID NO: 134)  
5'-GC GGC CTG GA-3' (FRAG 125) (SEQ. ID NO: 135)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 126) (SEQ. ID NO: 136)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 127) (SEQ. ID NO: 137)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 128) (SEQ. ID NO: 138)  
35 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 129) (SEQ. ID NO: 139)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 130) (SEQ. ID NO: 140)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 131) (SEQ. ID NO: 141)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG CAC AGG -3' (FRAG 132) (SEQ. ID NO: 142)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 133) (SEQ. ID NO: 143)  
40 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 134) (SEQ. ID NO: 144)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 135) (SEQ. ID NO: 145)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 136) (SEQ. ID NO: 146)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG C-3' (FRAG 137) (SEQ. ID NO: 147)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG -3' (FRAG 138) (SEQ. ID NO: 148)  
45 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GG-3' (FRAG 139) (SEQ. ID NO: 149)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC G-3' (FRAG 140) (SEQ. ID NO: 150)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC -3' (FRAG 141) (SEQ. ID NO: 151)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 142) (SEQ. ID NO: 152)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 143) (SEQ. ID NO: 153)  
50 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 144) (SEQ. ID NO: 154)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 145) (SEQ. ID NO: 155)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 146) (SEQ. ID NO: 156)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 147) (SEQ. ID NO: 157)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 148) (SEQ. ID NO: 158)  
55 5'-C GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 148) (SEQ. ID NO: 159)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 150) (SEQ. ID NO: 160)  
5'-C GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 151) (SEQ. ID NO: 161)  
5'-C GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 152) (SEQ. ID NO: 162)  
5'-C GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 153) (SEQ. ID NO: 163)  
60 5'-C GGC CTG GAA AGC TGA GAT GG -3' (FRAG 154) (SEQ. ID NO: 164)  
5'-C GGC CTG GAA AGC TGA GAT G -3' (FRAG 155) (SEQ. ID NO: 165)  
5'-C GGC CTG GAA AGC TGA GAT -3' (FRAG 156) (SEQ. ID NO: 166)  
5'-C GGC CTG GAA AGC TGA GA-3' (FRAG 157) (SEQ. ID NO: 167)  
5'-C GGC CTG GAA AGC TGA G-3' (FRAG 158) (SEQ. ID NO: 168)

- 5'-C GGC CTG GAA AGC TGA-3' (FRAG 159) (SEQ. ID NO: 169)  
5'-C GGC CTG GAA AGC TG-3' (FRAG 160) (SEQ. ID NO: 170)  
5'-C GGC CTG GAA AGC T-3' (FRAG 161) (SEQ. ID NO: 171)  
5'-C GGC CTG GAA AGC-3' (FRAG 162) (SEQ. ID NO: 172)  
5'-C GGC CTG GAA AG-3' (FRAG 163) (SEQ. ID NO: 173)  
5'-C GGC CTG GAA A-3' (FRAG 164) (SEQ. ID NO: 174)  
5'-C GGC CTG GAA-3' (FRAG 165) (SEQ. ID NO: 175)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 166) (SEQ. ID NO: 176)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 167) (SEQ. ID NO: 177)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 168) (SEQ. ID NO: 178)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 169) (SEQ. ID NO: 179)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 170) (SEQ. ID NO: 180)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 171) (SEQ. ID NO: 181)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 172) (SEQ. ID NO: 182)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 173) (SEQ. ID NO: 183)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 174) (SEQ. ID NO: 184)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 175) (SEQ. ID NO: 185)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 176) (SEQ. ID NO: 186)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 177) (SEQ. ID NO: 187)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 178) (SEQ. ID NO: 188)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 179) (SEQ. ID NO: 189)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 180) (SEQ. ID NO: 190)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 181) (SEQ. ID NO: 191)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 182) (SEQ. ID NO: 192)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 183) (SEQ. ID NO: 193)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 184) (SEQ. ID NO: 194)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 185) (SEQ. ID NO: 195)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 186) (SEQ. ID NO: 196)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 187) (SEQ. ID NO: 197)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 188) (SEQ. ID NO: 198)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 189) (SEQ. ID NO: 199)  
5'-GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 190) (SEQ. ID NO: 200)  
5'-GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 191) (SEQ. ID NO: 201)  
5'-GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 192) (SEQ. ID NO: 202)  
5'-GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 193) (SEQ. ID NO: 203)  
5'-GGC CTG GAA AGC TGA GAT GG -3' (FRAG 194) (SEQ. ID NO: 204)  
5'-GGC CTG GAA AGC TGA GAT G -3' (FRAG 195) (SEQ. ID NO: 205)  
5'-GGC CTG GAA AGC TGA GAT -3' (FRAG 196) (SEQ. ID NO: 206)  
5'-GGC CTG GAA AGC TGA GA-3' (FRAG 197) (SEQ. ID NO: 207)  
5'-GGC CTG GAA AGC TGA G-3' (FRAG 198) (SEQ. ID NO: 208)  
5'-GGC CTG GAA AGC TGA-3' (FRAG 199) (SEQ. ID NO: 209)  
5'-GGC CTG GAA AGC TG-3' (FRAG 200) (SEQ. ID NO: 210)  
5'-GGC CTG GAA AGC T-3' (FRAG 201) (SEQ. ID NO: 211)  
5'-GGC CTG GAA AGC-3' (FRAG 202) (SEQ. ID NO: 212)  
5'-GGC CTG GAA AG-3' (FRAG 203) (SEQ. ID NO: 213)  
5'-GGC CTG GAA A-3' (FRAG 204) (SEQ. ID NO: 214)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 205) (SEQ. ID NO: 215)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 206) (SEQ. ID NO: 216)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 207) (SEQ. ID NO: 217)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 208) (SEQ. ID NO: 218)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 209) (SEQ. ID NO: 219)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 210) (SEQ. ID NO: 220)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 211) (SEQ. ID NO: 221)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 212) (SEQ. ID NO: 222)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 213) (SEQ. ID NO: 223)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 214) (SEQ. ID NO: 224)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 215) (SEQ. ID NO: 225)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 216) (SEQ. ID NO: 226)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 217) (SEQ. ID NO: 227)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 218) (SEQ. ID NO: 228)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 219) (SEQ. ID NO: 229)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 220) (SEQ. ID NO: 230)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 221) (SEQ. ID NO: 231)  
5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 222) (SEQ. ID NO: 232)

- 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 223) (SEQ. ID NO: 233)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 224) (SEQ. ID NO: 234)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 225) (SEQ. ID NO: 235)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 226) (SEQ. ID NO: 236)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 227) (SEQ. ID NO: 237)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 228) (SEQ. ID NO: 238)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 229) (SEQ. ID NO: 239)  
 5'- GC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 230) (SEQ. ID NO: 240)  
 5'- GC CTG GAA AGC TGA GAT GGA G -3' (FRAG 231) (SEQ. ID NO: 241)  
 5'- GC CTG GAA AGC TGA GAT GGA -3' (FRAG 232) (SEQ. ID NO: 242)  
 5'- GC CTG GAA AGC TGA GAT GG -3' (FRAG 233) (SEQ. ID NO: 243)  
 5'- GC CTG GAA AGC TGA GAT G -3' (FRAG 234) (SEQ. ID NO: 244)  
 5'- GC CTG GAA AGC TGA GAT -3' (FRAG 235) (SEQ. ID NO: 245)  
 5'- GC CTG GAA AGC TGA GA-3' (FRAG 236) (SEQ. ID NO: 246)  
 5'- GC CTG GAA AGC TGA G-3' (FRAG 237) (SEQ. ID NO: 247)  
 5'- GC CTG GAA AGC TGA-3' (FRAG 238) (SEQ. ID NO: 248)  
 5'- GC CTG GAA AGC TG-3' (FRAG 239) (SEQ. ID NO: 249)  
 5'- GC CTG GAA AGC T-3' (FRAG 240) (SEQ. ID NO: 250)  
 5'- GC CTG GAA AGC-3' (FRAG 241) (SEQ. ID NO: 251)  
 5'- GC CTG GAA AG-3' (FRAG 242) (SEQ. ID NO: 252)  
 5'- C CTG GAA AGC TGA GAT GG A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 243) (SEQ. ID NO: 253)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 244) (SEQ. ID NO: 254)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 245) (SEQ. ID NO: 255)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 246) (SEQ. ID NO: 256)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 247) (SEQ. ID NO: 257)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 248) (SEQ. ID NO: 258)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 249) (SEQ. ID NO: 259)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 250) (SEQ. ID NO: 260)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 251) (SEQ. ID NO: 261)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 252) (SEQ. ID NO: 262)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 253) (SEQ. ID NO: 263)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 254) (SEQ. ID NO: 264)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 255) (SEQ. ID NO: 265)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 256) (SEQ. ID NO: 266)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 257) (SEQ. ID NO: 267)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 258) (SEQ. ID NO: 268)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 259) (SEQ. ID NO: 269)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 260) (SEQ. ID NO: 270)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 261) (SEQ. ID NO: 271)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 262) (SEQ. ID NO: 272)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 263) (SEQ. ID NO: 273)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 264) (SEQ. ID NO: 274)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 265) (SEQ. ID NO: 275)  
 5'- C CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 266) (SEQ. ID NO: 276)  
 5'- C CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 267) (SEQ. ID NO: 277)  
 5'- C CTG GAA AGC TGA GAT GGA GG -3' (FRAG 268) (SEQ. ID NO: 278)  
 5'- C CTG GAA AGC TGA GAT GGA G -3' (FRAG 269) (SEQ. ID NO: 279)  
 5'- C CTG GAA AGC TGA GAT GGA -3' (FRAG 270) (SEQ. ID NO: 280)  
 5'- C CTG GAA AGC TGA GAT GG -3' (FRAG 271) (SEQ. ID NO: 281)  
 5'- C CTG GAA AGC TGA GAT G -3' (FRAG 272) (SEQ. ID NO: 282)  
 5'- C CTG GAA AGC TGA GAT -3' (FRAG 273) (SEQ. ID NO: 283)  
 5'- C CTG GAA AGC TGA GA-3' (FRAG 274) (SEQ. ID NO: 284)  
 5'- C CTG GAA AGC TGA G-3' (FRAG 275) (SEQ. ID NO: 285)  
 5'- C CTG GAA AGC TGA-3' (FRAG 276) (SEQ. ID NO: 286)  
 5'- C CTG GAA AGC TG-3' (FRAG 277) (SEQ. ID NO: 287)  
 5'- C CTG GAA AGC T-3' (FRAG 278) (SEQ. ID NO: 288)  
 5'- C CTG GAA AGC-3' (FRAG 279) (SEQ. ID NO: 289)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 280) (SEQ. ID NO: 290)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 281) (SEQ. ID NO: 291)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 282) (SEQ. ID NO: 292)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 283) (SEQ. ID NO: 293)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 284) (SEQ. ID NO: 294)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 285) (SEQ. ID NO: 295)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 286) (SEQ. ID NO: 296)

- 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 287) (SEQ. ID NO: 297)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 288) (SEQ. ID NO: 298)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 289) (SEQ. ID NO: 299)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 290) (SEQ. ID NO: 300)  
 5 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 291) (SEQ. ID NO: 301)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 292) (SEQ. ID NO: 302)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 293) (SEQ. ID NO: 303)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 294) (SEQ. ID NO: 304)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 295) (SEQ. ID NO: 305)  
 10 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 296) (SEQ. ID NO: 306)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 297) (SEQ. ID NO: 307)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 298) (SEQ. ID NO: 308)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 299) (SEQ. ID NO: 309)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 300) (SEQ. ID NO: 310)  
 15 5'- CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 301) (SEQ. ID NO: 311)  
 5'- CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 302) (SEQ. ID NO: 312)  
 5'- CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 303) (SEQ. ID NO: 313)  
 5'- CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 304) (SEQ. ID NO: 314)  
 5'- CTG GAA AGC TGA GAT GGA GG -3' (FRAG 305) (SEQ. ID NO: 315)  
 20 5'- CTG GAA AGC TGA GAT GGA G -3' (FRAG 306) (SEQ. ID NO: 316)  
 5'- CTG GAA AGC TGA GAT GGA -3' (FRAG 307) (SEQ. ID NO: 317)  
 5'- CTG GAA AGC TGA GAT GG -3' (FRAG 308) (SEQ. ID NO: 318)  
 5'- CTG GAA AGC TGA GAT G -3' (FRAG 309) (SEQ. ID NO: 319)  
 5'- CTG GAA AGC TGA GAT -3' (FRAG 310) (SEQ. ID NO: 320)  
 25 5'- CTG GAA AGC TGA GA-3' (FRAG 311) (SEQ. ID NO: 321)  
 5'- CTG GAA AGC TGA G-3' (FRAG 312) (SEQ. ID NO: 322)  
 5'- CTG GAA AGC TGA-3' (FRAG 313) (SEQ. ID NO: 323)  
 5'- CTG GAA AGC TG-3' (FRAG 314) (SEQ. ID NO: 324)  
 5'- CTG GAA AGC T-3' (FRAG 315) (SEQ. ID NO: 325)  
 30 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 316) (SEQ. ID NO: 326)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 317) (SEQ. ID NO: 327)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 318) (SEQ. ID NO: 328)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 319) (SEQ. ID NO: 329)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 320) (SEQ. ID NO: 330)  
 35 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 321) (SEQ. ID NO: 331)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 322) (SEQ. ID NO: 332)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 323) (SEQ. ID NO: 333)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 324) (SEQ. ID NO: 334)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 325) (SEQ. ID NO: 335)  
 40 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 326) (SEQ. ID NO: 336)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 327) (SEQ. ID NO: 337)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 328) (SEQ. ID NO: 338)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 329) (SEQ. ID NO: 339)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 330) (SEQ. ID NO: 340)  
 45 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 331) (SEQ. ID NO: 341)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 332) (SEQ. ID NO: 342)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 333) (SEQ. ID NO: 343)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 334) (SEQ. ID NO: 344)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 335) (SEQ. ID NO: 345)  
 50 5'- TG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 336) (SEQ. ID NO: 346)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 337) (SEQ. ID NO: 347)  
 5'- TG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 338) (SEQ. ID NO: 348)  
 5'- TG GAA AGC TGA GAT GGA GGG C -3' (FRAG 339) (SEQ. ID NO: 349)  
 5'- TG GAA AGC TGA GAT GGA GGG -3' (FRAG 340) (SEQ. ID NO: 350)  
 55 5'- TG GAA AGC TGA GAT GGA GG -3' (FRAG 341) (SEQ. ID NO: 351)  
 5'- TG GAA AGC TGA GAT GGA G -3' (FRAG 342) (SEQ. ID NO: 352)  
 5'- TG GAA AGC TGA GAT GGA -3' (FRAG 343) (SEQ. ID NO: 353)  
 5'- TG GAA AGC TGA GAT GG -3' (FRAG 344) (SEQ. ID NO: 354)  
 5'- TG GAA AGC TGA GAT G -3' (FRAG 345) (SEQ. ID NO: 355)  
 60 5'- TG GAA AGC TGA GAT -3' (FRAG 346) (SEQ. ID NO: 356)  
 5'- TG GAA AGC TGA GA-3' (FRAG 347) (SEQ. ID NO: 357)  
 5'- TG GAA AGC TGA G-3' (FRAG 348) (SEQ. ID NO: 358)  
 5'- TG GAA AGC TGA-3' (FRAG 349) (SEQ. ID NO: 359)  
 5'- TG GAA AGC TG-3' (FRAG 350) (SEQ. ID NO: 360)

- 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 351) (SEQ. ID NO: 361)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 352) (SEQ. ID NO: 362)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 353) (SEQ. ID NO: 363)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 354) (SEQ. ID NO: 364)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 355) (SEQ. ID NO: 365)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 356) (SEQ. ID NO: 366)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 357) (SEQ. ID NO: 367)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 358) (SEQ. ID NO: 368)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 359) (SEQ. ID NO: 369)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 360) (SEQ. ID NO: 370)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 361) (SEQ. ID NO: 371)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 362) (SEQ. ID NO: 372)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 363) (SEQ. ID NO: 373)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 364) (SEQ. ID NO: 374)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 365) (SEQ. ID NO: 375)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 366) (SEQ. ID NO: 376)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 367) (SEQ. ID NO: 377)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 368) (SEQ. ID NO: 378)  
5'- G GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 369) (SEQ. ID NO: 379)  
5'- G GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 370) (SEQ. ID NO: 380)  
5'- G GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 371) (SEQ. ID NO: 381)  
5'- G GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 372) (SEQ. ID NO: 382)  
5'- G GAA AGC TGA GAT GGA GGG CG -3' (FRAG 373) (SEQ. ID NO: 383)  
5'- G GAA AGC TGA GAT GGA GGG C -3' (FRAG 374) (SEQ. ID NO: 384)  
5'- G GAA AGC TGA GAT GGA GGG -3' (FRAG 375) (SEQ. ID NO: 385)  
5'- G GAA AGC TGA GAT GGA GG -3' (FRAG 376) (SEQ. ID NO: 386)  
5'- G GAA AGC TGA GAT GGA G -3' (FRAG 377) (SEQ. ID NO: 387)  
5'- G GAA AGC TGA GAT GGA -3' (FRAG 378) (SEQ. ID NO: 388)  
5'- G GAA AGC TGA GAT GG -3' (FRAG 379) (SEQ. ID NO: 389)  
5'- G GAA AGC TGA GAT G -3' (FRAG 380) (SEQ. ID NO: 390)  
5'- G GAA AGC TGA GAT -3' (FRAG 381) (SEQ. ID NO: 391)  
5'- G GAA AGC TGA GA-3' (FRAG 382) (SEQ. ID NO: 392)  
5'- G GAA AGC TGA G-3' (FRAG 383) (SEQ. ID NO: 393)  
5'- G GAA AGC TGA-3' (FRAG 384) (SEQ. ID NO: 394)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 385) (SEQ. ID NO: 395)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 386) (SEQ. ID NO: 396)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 387) (SEQ. ID NO: 397)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 388) (SEQ. ID NO: 398)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 389) (SEQ. ID NO: 399)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 390) (SEQ. ID NO: 400)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 391) (SEQ. ID NO: 401)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 392) (SEQ. ID NO: 402)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 393) (SEQ. ID NO: 403)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 394) (SEQ. ID NO: 404)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 395) (SEQ. ID NO: 405)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 396) (SEQ. ID NO: 406)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 397) (SEQ. ID NO: 407)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 398) (SEQ. ID NO: 408)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 399) (SEQ. ID NO: 409)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 400) (SEQ. ID NO: 410)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 401) (SEQ. ID NO: 411)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 402) (SEQ. ID NO: 412)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 403) (SEQ. ID NO: 413)  
5'- GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 404) (SEQ. ID NO: 414)  
5'- GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 405) (SEQ. ID NO: 415)  
5'- GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 406) (SEQ. ID NO: 416)  
5'- GAA AGC TGA GAT GGA GGG CG -3' (FRAG 407) (SEQ. ID NO: 417)  
5'- GAA AGC TGA GAT GGA GGG C -3' (FRAG 408) (SEQ. ID NO: 418)  
5'- GAA AGC TGA GAT GGA GGG -3' (FRAG 409) (SEQ. ID NO: 419)  
5'- GAA AGC TGA GAT GGA GG -3' (FRAG 410) (SEQ. ID NO: 420)  
5'- GAA AGC TGA GAT GGA G -3' (FRAG 411) (SEQ. ID NO: 421)  
5'- GAA AGC TGA GAT GGA -3' (FRAG 412) (SEQ. ID NO: 422)  
5'- GAA AGC TGA GAT GG -3' (FRAG 413) (SEQ. ID NO: 423)  
5'- GAA AGC TGA GAT G -3' (FRAG 414) (SEQ. ID NO: 424)

- 5'- GAA AGC TGA GAT -3' (FRAG 415) (SEQ. ID NO: 425)  
 5'- GAA AGC TGA GA-3' (FRAG 416) (SEQ. ID NO: 426)  
 5'- GAA AGC TGA G-3' (FRAG 417) (SEQ. ID NO: 427)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 418) (SEQ. ID NO: 428)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 419) (SEQ. ID NO: 429)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 420) (SEQ. ID NO: 430)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 421) (SEQ. ID NO: 431)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 422) (SEQ. ID NO: 432)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 423) (SEQ. ID NO: 433)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 424) (SEQ. ID NO: 434)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 425) (SEQ. ID NO: 435)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 426) (SEQ. ID NO: 436)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 427) (SEQ. ID NO: 437)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 428) (SEQ. ID NO: 438)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 429) (SEQ. ID NO: 439)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 430) (SEQ. ID NO: 440)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 431) (SEQ. ID NO: 441)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 432) (SEQ. ID NO: 442)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 433) (SEQ. ID NO: 443)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 434) (SEQ. ID NO: 444)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 435) (SEQ. ID NO: 445)  
 5'- AA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 436) (SEQ. ID NO: 446)  
 5'- AA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 437) (SEQ. ID NO: 447)  
 5'- AA AGC TGA GAT GGA GGG CGG C-3' (FRAG 438) (SEQ. ID NO: 448)  
 5'- AA AGC TGA GAT GGA GGG CGG -3' (FRAG 439) (SEQ. ID NO: 449)  
 5'- AA AGC TGA GAT GGA GGG CG -3' (FRAG 440) (SEQ. ID NO: 450)  
 5'- AA AGC TGA GAT GGA GGG C -3' (FRAG 441) (SEQ. ID NO: 451)  
 5'- AA AGC TGA GAT GGA GGG -3' (FRAG 442) (SEQ. ID NO: 452)  
 5'- AA AGC TGA GAT GGA GG -3' (FRAG 443) (SEQ. ID NO: 453)  
 5'- AA AGC TGA GAT GGA G -3' (FRAG 444) (SEQ. ID NO: 454)  
 5'- AA AGC TGA GAT GGA -3' (FRAG 445) (SEQ. ID NO: 455)  
 5'- AA AGC TGA GAT GG -3' (FRAG 446) (SEQ. ID NO: 456)  
 5'- AA AGC TGA GAT G -3' (FRAG 447) (SEQ. ID NO: 457)  
 5'- AA AGC TGA GAT -3' (FRAG 448) (SEQ. ID NO: 458)  
 5'- AA AGC TGA GA-3' (FRAG 449) (SEQ. ID NO: 459)  
 5'- A AGC TGA GAT GGA GGG CG G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 450) (SEQ. ID NO: 460)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 451) (SEQ. ID NO: 461)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 452) (SEQ. ID NO: 462)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 453) (SEQ. ID NO: 463)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 454) (SEQ. ID NO: 464)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 455) (SEQ. ID NO: 465)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 456) (SEQ. ID NO: 466)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 457) (SEQ. ID NO: 467)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 458) (SEQ. ID NO: 468)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 459) (SEQ. ID NO: 469)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 460) (SEQ. ID NO: 470)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 461) (SEQ. ID NO: 471)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 462) (SEQ. ID NO: 472)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 463) (SEQ. ID NO: 473)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 464) (SEQ. ID NO: 474)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 465) (SEQ. ID NO: 475)  
 5'- A AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 466) (SEQ. ID NO: 476)  
 5'- A AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 467) (SEQ. ID NO: 477)  
 5'- A AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 468) (SEQ. ID NO: 478)  
 5'- A AGC TGA GAT GGA GGG CGG CA-3' (FRAG 469) (SEQ. ID NO: 479)  
 5'- A AGC TGA GAT GGA GGG CGG C-3' (FRAG 470) (SEQ. ID NO: 480)  
 5'- A AGC TGA GAT GGA GGG CGG -3' (FRAG 471) (SEQ. ID NO: 481)  
 5'- A AGC TGA GAT GGA GGG CG -3' (FRAG 472) (SEQ. ID NO: 482)  
 5'- A AGC TGA GAT GGA GGG C -3' (FRAG 473) (SEQ. ID NO: 483)  
 5'- A AGC TGA GAT GGA GGG -3' (FRAG 474) (SEQ. ID NO: 484)  
 5'- A AGC TGA GAT GGA GG -3' (FRAG 475) (SEQ. ID NO: 485)  
 5'- A AGC TGA GAT GGA G -3' (FRAG 476) (SEQ. ID NO: 486)  
 5'- A AGC TGA GAT GGA -3' (FRAG 477) (SEQ. ID NO: 487)  
 5'- A AGC TGA GAT GG -3' (FRAG 478) (SEQ. ID NO: 488)



- 5'- A AGC TGA GAT G -3' (FRAG 479) (SEQ. ID NO: 489)  
 5'- A AGC TGA GAT -3' (FRAG 480) (SEQ. ID NO: 490)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 481) (SEQ. ID NO: 491)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 482) (SEQ. ID NO: 492)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 483) (SEQ. ID NO: 493)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 484) (SEQ. ID NO: 494)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 485) (SEQ. ID NO: 495)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 486) (SEQ. ID NO: 496)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 487) (SEQ. ID NO: 497)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 488) (SEQ. ID NO: 498)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 489) (SEQ. ID NO: 499)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 490) (SEQ. ID NO: 500)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 491) (SEQ. ID NO: 501)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 492) (SEQ. ID NO: 502)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 493) (SEQ. ID NO: 503)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 494) (SEQ. ID NO: 504)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 495) (SEQ. ID NO: 505)  
 5'- AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 496) (SEQ. ID NO: 506)  
 5'- AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 497) (SEQ. ID NO: 507)  
 5'- AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 498) (SEQ. ID NO: 508)  
 5'- AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 499) (SEQ. ID NO: 509)  
 5'- AGC TGA GAT GGA GGG CGG CA-3' (FRAG 500) (SEQ. ID NO: 510)  
 5'- AGC TGA GAT GGA GGG CGG C-3' (FRAG 501) (SEQ. ID NO: 511)  
 5'- AGC TGA GAT GGA GGG CGG -3' (FRAG 502) (SEQ. ID NO: 512)  
 5'- AGC TGA GAT GGA GGG CG -3' (FRAG 503) (SEQ. ID NO: 513)  
 5'- AGC TGA GAT GGA GGG C -3' (FRAG 504) (SEQ. ID NO: 514)  
 5'- AGC TGA GAT GGA GGG -3' (FRAG 505) (SEQ. ID NO: 515)  
 5'- AGC TGA GAT GGA GG -3' (FRAG 506) (SEQ. ID NO: 516)  
 5'- AGC TGA GAT GGA G -3' (FRAG 507) (SEQ. ID NO: 517)  
 5'- AGC TGA GAT GGA -3' (FRAG 508) (SEQ. ID NO: 518)  
 5'- AGC TGA GAT GG -3' (FRAG 509) (SEQ. ID NO: 519)  
 5'- AGC TGA GAT G -3' (FRAG 510) (SEQ. ID NO: 520)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 511) (SEQ. ID NO: 521)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 512) (SEQ. ID NO: 522)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 513) (SEQ. ID NO: 523)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 514) (SEQ. ID NO: 524)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 515) (SEQ. ID NO: 525)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 516) (SEQ. ID NO: 526)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 517) (SEQ. ID NO: 527)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 518) (SEQ. ID NO: 528)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 519) (SEQ. ID NO: 529)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 520) (SEQ. ID NO: 530)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 521) (SEQ. ID NO: 531)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 522) (SEQ. ID NO: 532)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 523) (SEQ. ID NO: 533)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 524) (SEQ. ID NO: 534)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 525) (SEQ. ID NO: 535)  
 5'- GC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 526) (SEQ. ID NO: 536)  
 5'- GC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 527) (SEQ. ID NO: 537)  
 5'- GC TGA GAT GGA GGG CGG CAT G -3' (FRAG 528) (SEQ. ID NO: 538)  
 5'- GC TGA GAT GGA GGG CGG CAT -3' (FRAG 529) (SEQ. ID NO: 539)  
 5'- GC TGA GAT GGA GGG CGG CA-3' (FRAG 530) (SEQ. ID NO: 540)  
 5'- GC TGA GAT GGA GGG CGG C-3' (FRAG 531) (SEQ. ID NO: 541)  
 5'- GC TGA GAT GGA GGG CGG -3' (FRAG 532) (SEQ. ID NO: 542)  
 5'- GC TGA GAT GGA GGG CG -3' (FRAG 533) (SEQ. ID NO: 543)  
 5'- GC TGA GAT GGA GGG C -3' (FRAG 534) (SEQ. ID NO: 544)  
 5'- GC TGA GAT GGA GGG -3' (FRAG 535) (SEQ. ID NO: 545)  
 5'- GC TGA GAT GGA GG -3' (FRAG 536) (SEQ. ID NO: 546)  
 5'- GC TGA GAT GGA G -3' (FRAG 537) (SEQ. ID NO: 547)  
 5'- GC TGA GAT GGA -3' (FRAG 538) (SEQ. ID NO: 548)  
 5'- GC TGA GAT GG -3' (FRAG 539) (SEQ. ID NO: 549)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 540) (SEQ. ID NO: 550)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 541) (SEQ. ID NO: 551)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 542) (SEQ. ID NO: 552)

- 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 543) (SEQ. ID NO: 553)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 544) (SEQ. ID NO: 554)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 545) (SEQ. ID NO: 555)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 546) (SEQ. ID NO: 556)  
 5 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 547) (SEQ. ID NO: 557)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 548) (SEQ. ID NO: 558)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 549) (SEQ. ID NO: 559)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 550) (SEQ. ID NO: 560)  
 10 5'- C TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 551) (SEQ. ID NO: 561)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 552) (SEQ. ID NO: 562)  
 5'- C TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 553) (SEQ. ID NO: 563)  
 5'- C TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 554) (SEQ. ID NO: 564)  
 5'- C TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 555) (SEQ. ID NO: 565)  
 5'- C TGA GAT GGA GGG CGG CAT GG -3' (FRAG 556) (SEQ. ID NO: 566)  
 15 5'- C TGA GAT GGA GGG CGG CAT G -3' (FRAG 557) (SEQ. ID NO: 567)  
 5'- C TGA GAT GGA GGG CGG CAT -3' (FRAG 558) (SEQ. ID NO: 568)  
 5'- C TGA GAT GGA GGG CGG CA-3' (FRAG 559) (SEQ. ID NO: 569)  
 5'- C TGA GAT GGA GGG CGG C-3' (FRAG 560) (SEQ. ID NO: 570)  
 5'- C TGA GAT GGA GGG CGG -3' (FRAG 561) (SEQ. ID NO: 571)  
 20 5'- C TGA GAT GGA GGG CG -3' (FRAG 562) (SEQ. ID NO: 572)  
 5'- C TGA GAT GGA GGG C -3' (FRAG 563) (SEQ. ID NO: 573)  
 5'- C TGA GAT GGA GGG -3' (FRAG 564) (SEQ. ID NO: 574)  
 5'- C TGA GAT GGA GG -3' (FRAG 565) (SEQ. ID NO: 575)  
 5'- C TGA GAT GGA G -3' (FRAG 566) (SEQ. ID NO: 576)  
 25 5'- C TGA GAT GGA -3' (FRAG 567) (SEQ. ID NO: 577)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 568) (SEQ. ID NO: 578)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 569) (SEQ. ID NO: 579)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 570) (SEQ. ID NO: 580)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 571) (SEQ. ID NO: 581)  
 30 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 572) (SEQ. ID NO: 582)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 573) (SEQ. ID NO: 583)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 574) (SEQ. ID NO: 584)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 575) (SEQ. ID NO: 585)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 576) (SEQ. ID NO: 586)  
 35 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 577) (SEQ. ID NO: 587)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 578) (SEQ. ID NO: 588)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 579) (SEQ. ID NO: 589)  
 5'- TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 580) (SEQ. ID NO: 590)  
 5'- TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 581) (SEQ. ID NO: 591)  
 40 5'- TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 582) (SEQ. ID NO: 592)  
 5'- TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 583) (SEQ. ID NO: 593)  
 5'- TGA GAT GGA GGG CGG CAT GG -3' (FRAG 584) (SEQ. ID NO: 594)  
 5'- TGA GAT GGA GGG CGG CAT G -3' (FRAG 585) (SEQ. ID NO: 595)  
 5'- TGA GAT GGA GGG CGG CAT -3' (FRAG 586) (SEQ. ID NO: 596)  
 45 5'- TGA GAT GGA GGG CGG CA-3' (FRAG 587) (SEQ. ID NO: 597)  
 5'- TGA GAT GGA GGG CGG C-3' (FRAG 588) (SEQ. ID NO: 598)  
 5'- TGA GAT GGA GGG CGG -3' (FRAG 589) (SEQ. ID NO: 599)  
 5'- TGA GAT GGA GGG CG -3' (FRAG 590) (SEQ. ID NO: 600)  
 5'- TGA GAT GGA GGG C -3' (FRAG 591) (SEQ. ID NO: 601)  
 50 5'- TGA GAT GGA GGG -3' (FRAG 592) (SEQ. ID NO: 602)  
 5'- TGA GAT GGA GG -3' (FRAG 593) (SEQ. ID NO: 603)  
 5'- TGA GAT GGA G -3' (FRAG 594) (SEQ. ID NO: 604)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 595) (SEQ. ID NO: 605)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 596) (SEQ. ID NO: 606)  
 55 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 597) (SEQ. ID NO: 607)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 598) (SEQ. ID NO: 608)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 599) (SEQ. ID NO: 609)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 600) (SEQ. ID NO: 610)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 601) (SEQ. ID NO: 611)  
 60 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 602) (SEQ. ID NO: 612)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 603) (SEQ. ID NO: 613)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 604) (SEQ. ID NO: 614)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 605) (SEQ. ID NO: 615)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 606) (SEQ. ID NO: 616)

- 5'- GA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 607) (SEQ. ID NO: 617)  
5'- GA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 608) (SEQ. ID NO: 618)  
5'- GA GAT GGA GGG CGG CAT GGC G-3' (FRAG 609) (SEQ. ID NO: 619)  
5'- GA GAT GGA GGG CGG CAT GGC -3' (FRAG 610) (SEQ. ID NO: 620)  
5'- GA GAT GGA GGG CGG CAT GG -3' (FRAG 611) (SEQ. ID NO: 621)  
5'- GA GAT GGA GGG CGG CAT G -3' (FRAG 612) (SEQ. ID NO: 622)  
5'- GA GAT GGA GGG CGG CAT -3' (FRAG 613) (SEQ. ID NO: 623)  
5'- GA GAT GGA GGG CGG CA-3' (FRAG 614) (SEQ. ID NO: 624)  
5'- GA GAT GGA GGG CGG C-3' (FRAG 615) (SEQ. ID NO: 625)  
5'- GA GAT GGA GGG CGG -3' (FRAG 616) (SEQ. ID NO: 626)  
5'- GA GAT GGA GGG CG -3' (FRAG 617) (SEQ. ID NO: 627)  
5'- GA GAT GGA GGG C -3' (FRAG 618) (SEQ. ID NO: 628)  
5'- GA GAT GGA GGG -3' (FRAG 619) (SEQ. ID NO: 629)  
5'- GA GAT GGA GG -3' (FRAG 620) (SEQ. ID NO: 630)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 621) (SEQ. ID NO: 631)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 622) (SEQ. ID NO: 632)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 623) (SEQ. ID NO: 633)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 624) (SEQ. ID NO: 634)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 625) (SEQ. ID NO: 635)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 626) (SEQ. ID NO: 636)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 627) (SEQ. ID NO: 637)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 628) (SEQ. ID NO: 638)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 629) (SEQ. ID NO: 639)  
5'- A GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 630) (SEQ. ID NO: 640)  
5'- A GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 631) (SEQ. ID NO: 641)  
5'- A GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 632) (SEQ. ID NO: 642)  
5'- A GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 633) (SEQ. ID NO: 643)  
5'- A GAT GGA GGG CGG CAT GGC GG-3' (FRAG 634) (SEQ. ID NO: 644)  
5'- A GAT GGA GGG CGG CAT GGC G-3' (FRAG 635) (SEQ. ID NO: 645)  
5'- A GAT GGA GGG CGG CAT GGC -3' (FRAG 636) (SEQ. ID NO: 646)  
5'- A GAT GGA GGG CGG CAT GG -3' (FRAG 637) (SEQ. ID NO: 647)  
5'- A GAT GGA GGG CGG CAT G -3' (FRAG 638) (SEQ. ID NO: 648)  
5'- A GAT GGA GGG CGG CAT -3' (FRAG 639) (SEQ. ID NO: 649)  
5'- A GAT GGA GGG CGG CA-3' (FRAG 640) (SEQ. ID NO: 650)  
5'- A GAT GGA GGG CGG C-3' (FRAG 641) (SEQ. ID NO: 651)  
5'- A GAT GGA GGG CGG -3' (FRAG 642) (SEQ. ID NO: 652)  
5'- A GAT GGA GGG CG -3' (FRAG 643) (SEQ. ID NO: 653)  
5'- A GAT GGA GGG C -3' (FRAG 644) (SEQ. ID NO: 654)  
5'- A GAT GGA GGG -3' (FRAG 645) (SEQ. ID NO: 655)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 646) (SEQ. ID NO: 656)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 647) (SEQ. ID NO: 657)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 648) (SEQ. ID NO: 658)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 649) (SEQ. ID NO: 659)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 650) (SEQ. ID NO: 660)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 651) (SEQ. ID NO: 661)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 652) (SEQ. ID NO: 662)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 653) (SEQ. ID NO: 663)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 654) (SEQ. ID NO: 664)  
5'- GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 655) (SEQ. ID NO: 665)  
5'- GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 656) (SEQ. ID NO: 666)  
5'- GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 657) (SEQ. ID NO: 667)  
5'- GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 658) (SEQ. ID NO: 668)  
5'- GAT GGA GGG CGG CAT GGC GG-3' (FRAG 659) (SEQ. ID NO: 669)  
5'- GAT GGA GGG CGG CAT GGC G-3' (FRAG 660) (SEQ. ID NO: 670)  
5'- GAT GGA GGG CGG CAT GGC -3' (FRAG 661) (SEQ. ID NO: 671)  
5'- GAT GGA GGG CGG CAT GG -3' (FRAG 662) (SEQ. ID NO: 672)  
5'- GAT GGA GGG CGG CAT G -3' (FRAG 663) (SEQ. ID NO: 673)  
5'- GAT GGA GGG CGG CAT -3' (FRAG 664) (SEQ. ID NO: 674)  
5'- GAT GGA GGG CGG CA-3' (FRAG 665) (SEQ. ID NO: 675)  
5'- GAT GGA GGG CGG C-3' (FRAG 666) (SEQ. ID NO: 676)  
5'- GAT GGA GGG CGG -3' (FRAG 667) (SEQ. ID NO: 677)  
5'- GAT GGA GGG CG -3' (FRAG 668) (SEQ. ID NO: 678)  
5'- GAT GGA GGG C -3' (FRAG 669) (SEQ. ID NO: 679)  
5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 670) (SEQ. ID NO: 680)

5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 671) (SEQ. ID NO: 681)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 672) (SEQ. ID NO: 682)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 673) (SEQ. ID NO: 683)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 674) (SEQ. ID NO: 684)  
 5 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 675) (SEQ. ID NO: 685)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 676) (SEQ. ID NO: 686)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 677) (SEQ. ID NO: 687)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 678) (SEQ. ID NO: 688)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 679) (SEQ. ID NO: 689)  
 10 5'- AT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 680) (SEQ. ID NO: 690)  
 5'- AT GGA GGG CGG CAT GGC GGG C-3' (FRAG 681) (SEQ. ID NO: 691)  
 5'- AT GGA GGG CGG CAT GGC GGG -3' (FRAG 682) (SEQ. ID NO: 692)  
 5'- AT GGA GGG CGG CAT GGC GG-3' (FRAG 683) (SEQ. ID NO: 693)  
 5'- AT GGA GGG CGG CAT GGC G-3' (FRAG 684) (SEQ. ID NO: 694)  
 15 5'- AT GGA GGG CGG CAT GGC -3' (FRAG 685) (SEQ. ID NO: 695)  
 5'- AT GGA GGG CGG CAT GG -3' (FRAG 686) (SEQ. ID NO: 696)  
 5'- AT GGA GGG CGG CAT G -3' (FRAG 687) (SEQ. ID NO: 697)  
 5'- AT GGA GGG CGG CAT -3' (FRAG 688) (SEQ. ID NO: 698)  
 5'- AT GGA GGG CGG CA-3' (FRAG 689) (SEQ. ID NO: 699)  
 20 5'- AT GGA GGG CGG C-3' (FRAG 690) (SEQ. ID NO: 700)  
 5'- AT GGA GGG CGG -3' (FRAG 691) (SEQ. ID NO: 701)  
 5'- AT GGA GGG CG -3' (FRAG 692) (SEQ. ID NO: 702)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 693) (SEQ. ID NO: 703)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 694) (SEQ. ID NO: 704)  
 25 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 695) (SEQ. ID NO: 705)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 696) (SEQ. ID NO: 706)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 697) (SEQ. ID NO: 707)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 698) (SEQ. ID NO: 708)  
 5'- T GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 699) (SEQ. ID NO: 709)  
 30 5'- T GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 700) (SEQ. ID NO: 710)  
 5'- T GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 701) (SEQ. ID NO: 711)  
 5'- T GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 702) (SEQ. ID NO: 712)  
 5'- T GGA GGG CGG CAT GGC GGG CA-3' (FRAG 703) (SEQ. ID NO: 713)  
 5'- T GGA GGG CGG CAT GGC GGG C-3' (FRAG 704) (SEQ. ID NO: 714)  
 35 5'- T GGA GGG CGG CAT GGC GGG -3' (FRAG 705) (SEQ. ID NO: 715)  
 5'- T GGA GGG CGG CAT GGC GG-3' (FRAG 706) (SEQ. ID NO: 716)  
 5'- T GGA GGG CGG CAT GGC G-3' (FRAG 707) (SEQ. ID NO: 717)  
 5'- T GGA GGG CGG CAT GGC -3' (FRAG 708) (SEQ. ID NO: 718)  
 5'- T GGA GGG CGG CAT GG -3' (FRAG 709) (SEQ. ID NO: 719)  
 40 5'- T GGA GGG CGG CAT G -3' (FRAG 710) (SEQ. ID NO: 720)  
 5'- T GGA GGG CGG CAT -3' (FRAG 711) (SEQ. ID NO: 721)  
 5'- T GGA GGG CGG CA-3' (FRAG 712) (SEQ. ID NO: 722)  
 5'- T GGA GGG CGG C-3' (FRAG 713) (SEQ. ID NO: 723)  
 5'- T GGA GGG CGG -3' (FRAG 714) (SEQ. ID NO: 724)  
 45 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 715) (SEQ. ID NO: 725)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 716) (SEQ. ID NO: 726)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 717) (SEQ. ID NO: 727)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 718) (SEQ. ID NO: 728)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 719) (SEQ. ID NO: 729)  
 50 5'- GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 720) (SEQ. ID NO: 730)  
 5'- GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 721) (SEQ. ID NO: 731)  
 5'- GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 722) (SEQ. ID NO: 732)  
 5'- GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 723) (SEQ. ID NO: 733)  
 5'- GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 724) (SEQ. ID NO: 734)  
 55 5'- GGA GGG CGG CAT GGC GGG CA-3' (FRAG 725) (SEQ. ID NO: 735)  
 5'- GGA GGG CGG CAT GGC GGG C-3' (FRAG 726) (SEQ. ID NO: 736)  
 5'- GGA GGG CGG CAT GGC GGG -3' (FRAG 727) (SEQ. ID NO: 737)  
 5'- GGA GGG CGG CAT GGC GG-3' (FRAG 728) (SEQ. ID NO: 738)  
 5'- GGA GGG CGG CAT GGC G-3' (FRAG 729) (SEQ. ID NO: 739)  
 60 5'- GGA GGG CGG CAT GGC -3' (FRAG 730) (SEQ. ID NO: 740)  
 5'- GGA GGG CGG CAT GG -3' (FRAG 731) (SEQ. ID NO: 741)  
 5'- GGA GGG CGG CAT G -3' (FRAG 732) (SEQ. ID NO: 742)  
 5'- GGA GGG CGG CAT -3' (FRAG 733) (SEQ. ID NO: 743)  
 5'- GGA GGG CGG CA-3' (FRAG 734) (SEQ. ID NO: 744)

- 5'- GGA GGG CGG C-3' (FRAG 735) (SEQ. ID NO: 745)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 736) (SEQ. ID NO: 746)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 737) (SEQ. ID NO: 747)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 738) (SEQ. ID NO: 748)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 739) (SEQ. ID NO: 749)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 740) (SEQ. ID NO: 750)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 741) (SEQ. ID NO: 751)  
 5'- GA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 742) (SEQ. ID NO: 752)  
 5'- GA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 743) (SEQ. ID NO: 753)  
 5'- GA GGG CGG CAT GGC GGG CAC A-3' (FRAG 744) (SEQ. ID NO: 754)  
 5'- GA GGG CGG CAT GGC GGG CAC-3' (FRAG 745) (SEQ. ID NO: 755)  
 5'- GA GGG CGG CAT GGC GGG CA-3' (FRAG 746) (SEQ. ID NO: 756)  
 5'- GA GGG CGG CAT GGC GGG C-3' (FRAG 747) (SEQ. ID NO: 757)  
 5'- GA GGG CGG CAT GGC GGG -3' (FRAG 748) (SEQ. ID NO: 758)  
 5'- GA GGG CGG CAT GGC GG-3' (FRAG 749) (SEQ. ID NO: 759)  
 5'- GA GGG CGG CAT GGC G-3' (FRAG 750) (SEQ. ID NO: 760)  
 5'- GA GGG CGG CAT GGC -3' (FRAG 751) (SEQ. ID NO: 761)  
 5'- GA GGG CGG CAT GG -3' (FRAG 752) (SEQ. ID NO: 762)  
 5'- GA GGG CGG CAT G -3' (FRAG 753) (SEQ. ID NO: 763)  
 5'- GA GGG CGG CAT -3' (FRAG 754) (SEQ. ID NO: 764)  
 5'- GA GGG CGG CA-3' (FRAG 755) (SEQ. ID NO: 765)  
 5'- A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 756) (SEQ. ID NO: 766)  
 5'- A GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 757) (SEQ. ID NO: 767)  
 5'- A GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 758) (SEQ. ID NO: 768)  
 5'- A GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 759) (SEQ. ID NO: 769)  
 5'- A GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 760) (SEQ. ID NO: 770)  
 5'- A GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 761) (SEQ. ID NO: 771)  
 5'- A GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 762) (SEQ. ID NO: 772)  
 5'- A GGG CGG CAT GGC GGG CAC AG-3' (FRAG 763) (SEQ. ID NO: 773)  
 5'- A GGG CGG CAT GGC GGG CAC A-3' (FRAG 764) (SEQ. ID NO: 774)  
 5'- A GGG CGG CAT GGC GGG CAC-3' (FRAG 765) (SEQ. ID NO: 775)  
 5'- A GGG CGG CAT GGC GGG CA-3' (FRAG 766) (SEQ. ID NO: 776)  
 5'- A GGG CGG CAT GGC GGG C-3' (FRAG 767) (SEQ. ID NO: 777)  
 5'- A GGG CGG CAT GGC GGG -3' (FRAG 768) (SEQ. ID NO: 778)  
 5'- A GGG CGG CAT GGC GG-3' (FRAG 769) (SEQ. ID NO: 779)  
 5'- A GGG CGG CAT GGC G-3' (FRAG 770) (SEQ. ID NO: 780)  
 5'- A GGG CGG CAT GGC -3' (FRAG 771) (SEQ. ID NO: 781)  
 5'- A GGG CGG CAT GG -3' (FRAG 772) (SEQ. ID NO: 782)  
 5'- A GGG CGG CAT G -3' (FRAG 773) (SEQ. ID NO: 783)  
 5'- A GGG CGG CAT -3' (FRAG 774) (SEQ. ID NO: 784)  
 5'- GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 775) (SEQ. ID NO: 785)  
 5'- GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 776) (SEQ. ID NO: 786)  
 5'- GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 777) (SEQ. ID NO: 787)  
 5'- GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 778) (SEQ. ID NO: 788)  
 5'- GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 779) (SEQ. ID NO: 789)  
 5'- GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 780) (SEQ. ID NO: 790)  
 5'- GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 781) (SEQ. ID NO: 791)  
 5'- GGG CGG CAT GGC GGG CAC AG-3' (FRAG 782) (SEQ. ID NO: 792)  
 5'- GGG CGG CAT GGC GGG CAC A-3' (FRAG 783) (SEQ. ID NO: 793)  
 5'- GGG CGG CAT GGC GGG CAC-3' (FRAG 784) (SEQ. ID NO: 794)  
 5'- GGG CGG CAT GGC GGG CA-3' (FRAG 785) (SEQ. ID NO: 795)  
 5'- GGG CGG CAT GGC GGG C-3' (FRAG 786) (SEQ. ID NO: 796)  
 5'- GGG CGG CAT GGC GGG -3' (FRAG 787) (SEQ. ID NO: 797)  
 5'- GGG CGG CAT GGC GG-3' (FRAG 788) (SEQ. ID NO: 798)  
 5'- GGG CGG CAT GGC G-3' (FRAG 789) (SEQ. ID NO: 799)  
 5'- GGG CGG CAT GGC -3' (FRAG 790) (SEQ. ID NO: 800)  
 5'- GGG CGG CAT GG -3' (FRAG 791) (SEQ. ID NO: 801)  
 5'- GGG CGG CAT G -3' (FRAG 792) (SEQ. ID NO: 802)  
 5'- GG CGG CAT GGC GGG CAC AG G CTG GGC-3' (FRAG 793) (SEQ. ID NO: 803)  
 5'- GG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 794) (SEQ. ID NO: 804)  
 5'- GG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 795) (SEQ. ID NO: 805)  
 5'- GG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 796) (SEQ. ID NO: 806)  
 5'- GG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 797) (SEQ. ID NO: 807)  
 5'- GG CGG CAT GGC GGG CAC AGG C-3' (FRAG 798) (SEQ. ID NO: 808)

- 5'- GG CGG CAT GGC GGG CAC AGG -3' (FRAG 799) (SEQ. ID NO: 809)  
 5'- GG CGG CAT GGC GGG CAC AG-3' (FRAG 800) (SEQ. ID NO: 810)  
 5'- GG CGG CAT GGC GGG CAC A-3' (FRAG 801) (SEQ. ID NO: 811)  
 5'- GG CGG CAT GGC GGG CAC-3' (FRAG 802) (SEQ. ID NO: 812)  
 5'- GG CGG CAT GGC GGG CA-3' (FRAG 803) (SEQ. ID NO: 813)  
 5'- GG CGG CAT GGC GGG C-3' (FRAG 804) (SEQ. ID NO: 814)  
 5'- GG CGG CAT GGC GGG -3' (FRAG 805) (SEQ. ID NO: 815)  
 5'- GG CGG CAT GGC GGG-3' (FRAG 806) (SEQ. ID NO: 816)  
 5'- GG CGG CAT GGC G-3' (FRAG 807) (SEQ. ID NO: 817)  
 5'- GG CGG CAT GGC -3' (FRAG 808) (SEQ. ID NO: 818)  
 5'- GG CGG CAT GG -3' (FRAG 809) (SEQ. ID NO: 819)  
 5'- G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 810) (SEQ. ID NO: 820)  
 5'- G CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 811) (SEQ. ID NO: 821)  
 5'- G CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 812) (SEQ. ID NO: 822)  
 5'- G CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 813) (SEQ. ID NO: 823)  
 5'- G CGG CAT GGC GGG CAC AGG CT-3' (FRAG 814) (SEQ. ID NO: 824)  
 5'- G CGG CAT GGC GGG CAC AGG C-3' (FRAG 815) (SEQ. ID NO: 825)  
 5'- G CGG CAT GGC GGG CAC AGG -3' (FRAG 816) (SEQ. ID NO: 826)  
 5'- G CGG CAT GGC GGG CAC AG-3' (FRAG 817) (SEQ. ID NO: 827)  
 5'- G CGG CAT GGC GGG CAC A-3' (FRAG 818) (SEQ. ID NO: 828)  
 5'- G CGG CAT GGC GGG CAC-3' (FRAG 819) (SEQ. ID NO: 829)  
 5'- G CGG CAT GGC GGG CA-3' (FRAG 820) (SEQ. ID NO: 830)  
 5'- G CGG CAT GGC GGG C-3' (FRAG 821) (SEQ. ID NO: 831)  
 5'- G CGG CAT GGC GGG -3' (FRAG 822) (SEQ. ID NO: 832)  
 5'- G CGG CAT GGC GG-3' (FRAG 823) (SEQ. ID NO: 833)  
 5'- G CGG CAT GGC G-3' (FRAG 824) (SEQ. ID NO: 834)  
 5'- G CGG CAT GGC -3' (FRAG 825) (SEQ. ID NO: 835)  
 5'- CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 826) (SEQ. ID NO: 836)  
 5'- CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 827) (SEQ. ID NO: 837)  
 5'- CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 828) (SEQ. ID NO: 838)  
 5'- CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 829) (SEQ. ID NO: 839)  
 5'- CGG CAT GGC GGG CAC AGG CT-3' (FRAG 830) (SEQ. ID NO: 840)  
 5'- CGG CAT GGC GGG CAC AGG C-3' (FRAG 831) (SEQ. ID NO: 841)  
 5'- CGG CAT GGC GGG CAC AGG -3' (FRAG 832) (SEQ. ID NO: 842)  
 5'- CGG CAT GGC GGG CAC AG-3' (FRAG 833) (SEQ. ID NO: 843)  
 5'- CGG CAT GGC GGG CAC A-3' (FRAG 834) (SEQ. ID NO: 844)  
 5'- CGG CAT GGC GGG CAC-3' (FRAG 835) (SEQ. ID NO: 845)  
 5'- CGG CAT GGC GGG CA-3' (FRAG 836) (SEQ. ID NO: 846)  
 5'- CGG CAT GGC GGG C-3' (FRAG 837) (SEQ. ID NO: 847)  
 5'- CGG CAT GGC GGG -3' (FRAG 838) (SEQ. ID NO: 848)  
 5'- CGG CAT GGC GG-3' (FRAG 839) (SEQ. ID NO: 849)  
 5'- CGG CAT GGC G-3' (FRAG 840) (SEQ. ID NO: 850)  
 5'- GG CAT GGC GGG CAC AGG C TG GGC-3' (FRAG 841) (SEQ. ID NO: 851)  
 5'- GG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 842) (SEQ. ID NO: 852)  
 5'- GG CAT GGC GGG CAC AGG CTG G-3' (FRAG 843) (SEQ. ID NO: 853)  
 5'- GG CAT GGC GGG CAC AGG CTG -3' (FRAG 844) (SEQ. ID NO: 854)  
 5'- GG CAT GGC GGG CAC AGG CT-3' (FRAG 845) (SEQ. ID NO: 855)  
 5'- GG CAT GGC GGG CAC AGG C-3' (FRAG 846) (SEQ. ID NO: 856)  
 5'- GG CAT GGC GGG CAC AGG -3' (FRAG 847) (SEQ. ID NO: 857)  
 5'- GG CAT GGC GGG CAC AG-3' (FRAG 848) (SEQ. ID NO: 858)  
 5'- GG CAT GGC GGG CAC A-3' (FRAG 849) (SEQ. ID NO: 859)  
 5'- GG CAT GGC GGG CAC-3' (FRAG 850) (SEQ. ID NO: 860)  
 5'- GG CAT GGC GGG CA-3' (FRAG 851) (SEQ. ID NO: 861)  
 5'- GG CAT GGC GGG C-3' (FRAG 852) (SEQ. ID NO: 862)  
 5'- GG CAT GGC GGG -3' (FRAG 853) (SEQ. ID NO: 863)  
 5'- GG CAT GGC GG-3' (FRAG 854) (SEQ. ID NO: 864)  
 5'- G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 855) (SEQ. ID NO: 865)  
 5'- G CAT GGC GGG CAC AGG CTG GG-3' (FRAG 856) (SEQ. ID NO: 866)  
 5'- G CAT GGC GGG CAC AGG CTG G-3' (FRAG 857) (SEQ. ID NO: 867)  
 5'- G CAT GGC GGG CAC AGG CTG -3' (FRAG 858) (SEQ. ID NO: 868)  
 5'- G CAT GGC GGG CAC AGG CT-3' (FRAG 859) (SEQ. ID NO: 869)  
 5'- G CAT GGC GGG CAC AGG C-3' (FRAG 860) (SEQ. ID NO: 870)  
 5'- G CAT GGC GGG CAC AGG -3' (FRAG 861) (SEQ. ID NO: 871)  
 5'- G CAT GGC GGG CAC AG-3' (FRAG 862) (SEQ. ID NO: 872)

5'- G CAT GGC GGG CAC A-3' (FRAG 863) (SEQ. ID NO: 873)  
 5'- G CAT GGC GGG CAC-3' (FRAG 864) (SEQ. ID NO: 874)  
 5'- G CAT GGC GGG CA-3' (FRAG 865) (SEQ. ID NO: 875)  
 5'- G CAT GGC GGG C-3' (FRAG 866) (SEQ. ID NO: 876)  
 5 G 5'- G CAT GGC GGG -3' (FRAG 867) (SEQ. ID NO: 877)  
 5'- CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 868) (SEQ. ID NO: 878)  
 5'- CAT GGC GGG CAC AGG CTG GG-3' (FRAG 869) (SEQ. ID NO: 879)  
 5'- CAT GGC GGG CAC AGG CTG G-3' (FRAG 870) (SEQ. ID NO: 880)  
 5'- CAT GGC GGG CAC AGG CTG -3' (FRAG 871) (SEQ. ID NO: 881)  
 10 5'- CAT GGC GGG CAC AGG CT-3' (FRAG 872) (SEQ. ID NO: 882)  
 5'- CAT GGC GGG CAC AGG C-3' (FRAG 873) (SEQ. ID NO: 883)  
 5'- CAT GGC GGG CAC AGG -3' (FRAG 874) (SEQ. ID NO: 884)  
 5'- CAT GGC GGG CAC AG-3' (FRAG 875) (SEQ. ID NO: 885)  
 5'- CAT GGC GGG CAC A-3' (FRAG 876) (SEQ. ID NO: 886)  
 15 5'- CAT GGC GGG CAC-3' (FRAG 877) (SEQ. ID NO: 887)  
 5'- CAT GGC GGG CA-3' (FRAG 878) (SEQ. ID NO: 888)  
 5'- CAT GGC GGG C-3' (FRAG 879) (SEQ. ID NO: 889)  
 5'- AT GGC GGG CAC AGG CTG GGC-3' (FRAG 880) (SEQ. ID NO: 890)  
 5'- AT GGC GGG CAC AGG CTG GG-3' (FRAG 881) (SEQ. ID NO: 891)  
 20 5'- AT GGC GGG CAC AGG CTG G-3' (FRAG 882) (SEQ. ID NO: 892)  
 5'- AT GGC GGG CAC AGG CTG -3' (FRAG 883) (SEQ. ID NO: 893)  
 5'- AT GGC GGG CAC AGG CT-3' (FRAG 884) (SEQ. ID NO: 894)  
 5'- AT GGC GGG CAC AGG C-3' (FRAG 885) (SEQ. ID NO: 895)  
 5'- AT GGC GGG CAC AGG -3' (FRAG 886) (SEQ. ID NO: 896)  
 25 5'- AT GGC GGG CAC AG-3' (FRAG 887) (SEQ. ID NO: 897)  
 5'- AT GGC GGG CAC A-3' (FRAG 888) (SEQ. ID NO: 898)  
 5'- AT GGC GGG CAC-3' (FRAG 889) (SEQ. ID NO: 899)  
 5'- AT GGC GGG CA-3' (FRAG 890) (SEQ. ID NO: 900)  
 5'- T GGC GGG CAC AGG CTG GGC-3' (FRAG 891) (SEQ. ID NO: 901)  
 30 5'- T GGC GGG CAC AGG CTG GG-3' (FRAG 892) (SEQ. ID NO: 902)  
 5'- T GGC GGG CAC AGG CTG G-3' (FRAG 893) (SEQ. ID NO: 903)  
 5'- T GGC GGG CAC AGG CTG -3' (FRAG 894) (SEQ. ID NO: 904)  
 5'- T GGC GGG CAC AGG CT-3' (FRAG 895) (SEQ. ID NO: 905)  
 5'- T GGC GGG CAC AGG C-3' (FRAG 896) (SEQ. ID NO: 906)  
 35 5'- T GGC GGG CAC AGG -3' (FRAG 897) (SEQ. ID NO: 907)  
 5'- T GGC GGG CAC AG-3' (FRAG 898) (SEQ. ID NO: 908)  
 5'- T GGC GGG CAC A-3' (FRAG 899) (SEQ. ID NO: 909)  
 5'- T GGC GGG CAC-3' (FRAG 900) (SEQ. ID NO: 910)  
 5'- GGC GGG CAC AGG CTG GGC-3' (FRAG 901) (SEQ. ID NO: 911)  
 40 5'- GGC GGG CAC AGG CTG GG-3' (FRAG 902) (SEQ. ID NO: 912)  
 5'- GGC GGG CAC AGG CTG G-3' (FRAG 903) (SEQ. ID NO: 913)  
 5'- GGC GGG CAC AGG CTG -3' (FRAG 904) (SEQ. ID NO: 914)  
 5'- GGC GGG CAC AGG CT-3' (FRAG 905) (SEQ. ID NO: 915)  
 5'- GGC GGG CAC AGG C-3' (FRAG 906) (SEQ. ID NO: 916)  
 45 5'- GGC GGG CAC AGG -3' (FRAG 907) (SEQ. ID NO: 917)  
 5'- GGC GGG CAC AG-3' (FRAG 908) (SEQ. ID NO: 918)  
 5'- GGC GGG CAC A-3' (FRAG 909) (SEQ. ID NO: 919)  
 5'- GC GGG CAC AGG CTG GGC-3' (FRAG 910) (SEQ. ID NO: 920)  
 5'- GC GGG CAC AGG CTG GG-3' (FRAG 911) (SEQ. ID NO: 921)  
 50 5'- GC GGG CAC AGG CTG G-3' (FRAG 912) (SEQ. ID NO: 922)  
 5'- GC GGG CAC AGG CTG -3' (FRAG 913) (SEQ. ID NO: 923)  
 5'- GC GGG CAC AGG CT-3' (FRAG 914) (SEQ. ID NO: 924)  
 5'- GC GGG CAC AGG C-3' (FRAG 915) (SEQ. ID NO: 925)  
 5'- GC GGG CAC AGG -3' (FRAG 916) (SEQ. ID NO: 926)  
 55 5'- GC GGG CAC AG-3' (FRAG 917) (SEQ. ID NO: 927)  
 5'- C GGG CAC AGG CTG GGC-3' (FRAG 918) (SEQ. ID NO: 928)  
 5'- GGG CAC AGG CTG GG-3' (FRAG 919) (SEQ. ID NO: 929)  
 5'- C GGG CAC AGG CTG G-3' (FRAG 920) (SEQ. ID NO: 930)  
 5'- C GGG CAC AGG CTG -3' (FRAG 921) (SEQ. ID NO: 931)  
 60 5'- C GGG CAC AGG CT-3' (FRAG 922) (SEQ. ID NO: 932)  
 5'- C GGG CAC AGG C-3' (FRAG 923) (SEQ. ID NO: 933)  
 5'- C GGG CAC AGG -3' (FRAG 924) (SEQ. ID NO: 934)  
 5'- GGG CAC AGG CTG GGC-3' (FRAG 925) (SEQ. ID NO: 935)  
 5'- GGG CAC AGG CTG GG-3' (FRAG 926) (SEQ. ID NO: 936)

- 5'- GGG CAC AGG CTG G-3' (FRAG 927) (SEQ. ID NO: 937)  
 5'- GGG CAC AGG CTG -3' (FRAG 928) (SEQ. ID NO: 938)  
 5'- GGG CAC AGG CT-3' (FRAG 929) (SEQ. ID NO: 939)  
 5'- GGG CAC AGG C-3' (FRAG 930) (SEQ. ID NO: 940)  
 5 5'- GG CAC AGG CTG GGC-3' (FRAG 931) (SEQ. ID NO: 941)  
 5'- GG CAC AGG CTG GG-3' (FRAG 932) (SEQ. ID NO: 942)  
 5'- GG CAC AGG CTG G-3' (FRAG 933) (SEQ. ID NO: 943)  
 5'- GG CAC AGG CTG -3' (FRAG 934) (SEQ. ID NO: 944)  
 5'- GG CAC AGG CT-3' (FRAG 935) (SEQ. ID NO: 945)  
 10 5'- G CAC AGG CTG GGC-3' (FRAG 936) (SEQ. ID NO: 946)  
 5'- G CAC AGG CTG GG-3' (FRAG 937) (SEQ. ID NO: 947)  
 5'- G CAC AGG CTG G-3' (FRAG 938) (SEQ. ID NO: 948)  
 5'- G CAC AGG CTG -3' (FRAG 939) (SEQ. ID NO: 949)  
 5'- CAC AGG CTG GGC-3' (FRAG 940) (SEQ. ID NO: 950)  
 15 5'- CAC AGG CTG GG-3' (FRAG 941) (SEQ. ID NO: 951)  
 5'-CAC AGG CTG G-3' (FRAG 942) (SEQ. ID NO: 952)  
 5'-AC AGG CTG GGC-3' (FRAG 943) (SEQ. ID NO: 953)  
 5'-AC AGG CTG GG-3' (FRAG 944) (SEQ. ID NO: 954)  
 5'-C AGG CTG GGC-3' (FRAG 945) (SEQ. ID NO: 955)  
 20 5'-TTT TCC TTC CTT TGT CTC TCT TC (FRAG 946) (SEQ. ID NO: 956)  
 5'-GCT CCC GGC TGC CTG (FRAG 947) (SEQ. ID NO: 957)  
 5'-CTC GGC CGT GCG GCT CTG TCG CTC CCG GT (FRAG 948) (SEQ. ID NO: 958)  
 5'-CCG CCG CCC TCC GGG GGC TC (FRAG 949) (SEQ. ID NO: 959)  
 5'-TGC TGC CGT TGG CTG CCC (FRAG 950) (SEQ. ID NO: 960)  
 25 5'-CTT CTG CGG GTC GCC GG (FRAG 951) (SEQ. ID NO: 961)  
 5'-TGC TGG GCT TGT GGC (FRAG 952) (SEQ. ID NO: 962)  
 5'-GGC CTC TCT TCT GGC (FRAG 953) (SEQ. ID NO: 963)  
 5'-CCT GGT CCC TCC GT (FRAG 954) (SEQ. ID NO: 964)  
 5'-GGT GGC TCC TCT GC (FRAG 955) (SEQ. ID NO: 965)  
 30 5'-GCT TGG TCC TGG GGC TGC (FRAG 956) (SEQ. ID NO: 966)  
 5'-TGC TCT CCT CTC CTT (FRAG 957) (SEQ. ID NO: 967)

#### Human Adenosine A2a Receptor Anti-sense Oligonucleotide Fragments

- 5'-TGC TTT TCT TTT CTG GGC CTC TGT GGT CTG TTT TTT TCT G GCC CTG CTG GGG CGC TCT CC GCC GCC CGC CTG  
 GCT CCC GGB GCC CBT GBT GGG CBT GCC GTG GTT CTT GCC CTC CTT TGG CTG CCG TGC CCG CTC CCC GGC CTC CTG  
 35 GCG GGT GGC CGT TG GGC CCG TGT TCC CCT GGG -GCC TGG GGC TCC CTT CTC TC GCC CTT CTT GCT GGG CCT C TGC  
 TGC TGC TGG TGC TGT GGC CCC C GTA CAC CGA GGA GCC CAT GAT GGG CAT GCC ACA GAC GAC AGG C GTB CBC  
 CGB GGB GCC CBT GBT GGG CBT GCC BCB GBC GBC BGG C-3' (FRAG. NO. 1665) (SEQ. ID NO:1678)  
 5'-CTG GGC CTC-3' (FRAG 1666) (SEQ. ID NO: 1679)  
 5'-GCC GCC CGC CTG-3' (FRAG 1667) (SEQ. ID NO: 1680)  
 40 5'-GC CCG CTC CCC GGC-3' (FRAG 1668) (SEQ. ID NO: 1681)  
 5'-CBCCGBGGBGCCC-3' (FRAG 1669) (SEQ. ID NO: 1682)  
 5'-TGC TTT TCT TTT CTG GGC CTC-3' (FRAG 958) (SEQ. ID NO: 968)  
 5'-TGT GGT CTG TTT TTT TCT G-3' (FRAG 959) (SEQ. ID NO: 969)  
 5'-GCC CTG CTG GGG CGC TCT CC-3' (FRAG 960) (SEQ. ID NO: 970)  
 45 5'-GCC GCC CGC CTG GCT CCC-3' (FRAG 961) (SEQ. ID NO: 971)  
 5'-GGB GCC CBT GBT GGG CBT GCC-3' (FRAG 962) (SEQ. ID NO: 972)  
 5'-GTG GTT CTT GCC CTC CTT TGG CTG-3' (FRAG 963) (SEQ. ID NO: 973)  
 5'-CCG TGC CCG CTC CCC GGC-3' (FRAG 964) (SEQ. ID NO: 974)  
 5'-CTC CTG GCG GGT GGC CGT TG-3' (FRAG 965) (SEQ. ID NO: 975)  
 50 5'-GGC CCG TGT TCC CCT GGG-3' (FRAG 966) (SEQ. ID NO: 976)  
 5'-GCC TGG GGC TCC CTT CTC TC-3' (FRAG 967) (SEQ. ID NO: 977)  
 5'-GCC CTT CTT GCT GGG CCT C-3' (FRAG 968) (SEQ. ID NO: 978)  
 5'-TGC TGC TGC TGG TGC TGT GGC CCC C-3' (FRAG 969) (SEQ. ID NO: 979)  
 5'-GTACACCGAGGAGCCCATGATGGGCATGCCACAGACGACAGGC-3' (FRAG 970) (SEQ. ID NO: 980)  
 55 5'-GTBCBCCGBGGBGCCCBTGGGCBTGCBCBGBCBGGC-3' (FRAG 971) (SEQ. ID NO: 981)

#### Human Adenosine A2b Receptor Anti-sense Oligonucleotide Fragments

5'-GGC GCC GTG CCG CGT CTT GGT GGC GGC GG GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC GTT CGC GCC CGC  
 CCG GGG CCC CTC CGG TCC CGG GTC GGG GCC CCC CGC GGC C GCC TCG GGG CTG GGG CGC TGG TGG CCG GG CCG



- CGC CTC CGC CTG CCG CTT CTG GCT GGG CCC CGG GCG CCC CCT CCC CTC TTG CTC GGG TCC CCG TG ACA GCG CGT  
 CCT GTG TCT CCA GCA GCA TGG CCG GGC CAG CTG GGC CCC BCB GCG CGT CCT GTG TCT CCB GCB GCB TGG CCG GGC  
 CBG CTG GGC CCC-3' (FRAG. NO: 1670) (SEQ. ID NO: 1683)  
 5'-GCGCGTCCTG-3' (FRAG. NO: 1671) (SEQ. ID NO: 1684)  
 5'-GCT GGG CCC CGG-3' (FRAG. NO: 1672) (SEQ. ID NO: 1685)  
 5'-CGG GTC GGG GCC CCC C-3' (FRAG. NO: 1673) (SEQ. ID NO: 1686)  
 5'-CGC GCC CGC G-3' (FRAG. NO: 1674) (SEQ. ID NO: 1687)  
 5'-GGC GCC GTG CCG CGT CTT GGT GGC GGC GG-3' (FRAG 972) (SEQ. ID NO: 982)  
 5'-GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC-3' (FRAG 973) (SEQ. ID NO: 983)  
 10 5'-GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC-3' (FRAG 974) (SEQ. ID NO: 984)  
 5'-CGG GTC GGG GCC CCC CGC GGC C-3' (FRAG 975) (SEQ. ID NO: 985)  
 5'-GCC TCG GGG CTG GGG CGC TGG TGG CCG GG-3' (FRAG 976) (SEQ. ID NO: 986)  
 5'-CCG CGC CTC CGC CTG CCG CTT CTG-3' (FRAG 977) (SEQ. ID NO: 987)  
 5'-GCT GGG CCC CGG GCG CCC CCT-3' (FRAG 978) (SEQ. ID NO: 988)  
 15 5'-CCC CTC TTG CTC GGG TCC CCG TG-3' (FRAG 979) (SEQ. ID NO: 989)  
 5'-ACAGCGCGTCTGTCTCTCCAGCAGCATGGCCGGGCGAGCTGGGCCCC-3' (FRAG 980) (SEQ. ID NO: 990)  
 5'-BCBGC CGCTCTGTCTCCBGCBCBTGGCCGGGCCBGTGGGCCCC-3' (FRAG 981) (SEQ. ID NO: 991)

### Human Adenosine A3 Receptor Anti-sense Oligonucleotide Fragments

- 5'-ACA GAG CAG TGC TGT TGT TGG GCA TCT TGC CTT CCC AGG G BCB GBG CB TGC TGT TGT TGG GCB TCT TGC CTT  
 20 CCC BGG GCC CTT TTC TGG TGG GGT GGT GCT GTT GTT GGG CTT TCT TCT GTT CCC BCB GBG CBG TGC TGT TGT TGG  
 GCB TCT TGC CTT CCC BGG GCC CTT TTC TGG TGG GGT GGT GCT GTT GTT GGG C TTT CTT CTG TTC CC (FRAG.  
 NO: 1675) (SEQ. ID NO: 1688)  
 5'-GBG CB TGC-3' (FRAG. NO: 1676) (SEQ. ID NO: 1689)  
 5'-TTG TTG GGC-3' (FRAG. NO: 1677) (SEQ. ID NO: 1690)  
 25 5'-TGC CTT CCC BGG G-3' (FRAG. NO: 1678) (SEQ. ID NO: 1691)  
 5'-GTT GTT GGG CAT CTT GCC-3' (FRAG. NO: 1679) (SEQ. ID NO: 1692)  
 5'-GTG GGC CTA GCT CTC GCC-3' (FRAG. NO: 1680) (SEQ. ID NO: 1693)  
 5'-ACA GAG CA TGC TGT TGT TGG GCA TCT TGC CTT CCC AGG G-3' (FRAG 982) (SEQ. ID NO: 992)  
 5'-BCB GBG CB TGC TGT TGT TGG GCB TCT TGC CTT CCC BGG G-3' (FRAG 983) (SEQ. ID NO: 993)  
 30 5'-CCC TTT TCT GGT GGG GTG-3' (FRAG 984) (SEQ. ID NO: 994)  
 5'-GTG CTG TTG TTG GGC-3' (FRAG 985) (SEQ. ID NO: 995)  
 5'-TTT CTT CTG TTC CC-3' (FRAG 986) (SEQ. ID NO: 996)  
 5'-CCC TTT TCT GGT GGG GTG-3' (FRAG 987) (SEQ. ID NO: 997)  
 5'-GTG CTG TTG TTG GGC-3' (FRAG 988) (SEQ. ID NO: 998)  
 35 5'-TTT CTT CTG TTC CC-3' (FRAG 989) (SEQ. ID NO: 999)

### Human IgE Receptor $\beta$ Anti-sense Oligonucleotide Fragments

- 5'-TTT CCC CTG GGT CTT CC CTC CTG CTC TTT TTT C ATT TGC TCT CCT ATT ACT TTC TGT GTC CAT TTT TTC ATT  
 AAC CGA GCT GT BTT TGC TCT CCT BTT BCT TTC TGT GTC CBT TTT TTC BTT BBC CGB GCT GT-3' (FRAG. NO: 1681)  
 (SEQ. ID NO: 1692)  
 40 5'-CCC CTG GG-3' (FRAG. NO: 1682) (SEQ. ID NO: 1693)  
 5'-GCTCTCCTBTT-3' (FRAG. NO: 1683) (SEQ. ID NO: 1694)  
 5'-CBTTBCCGCGCTG-3' (FRAG. NO: 1684) (SEQ. ID NO: 1695)  
 5'-TTT CCC CTG GGT CTT CC-3' (FRAG 990) (SEQ. ID NO: 1000)  
 5'-CTC CTG CTC TTT TTT C-3' (FRAG 991) (SEQ. ID NO: 1001)  
 45 ATTTGCTCTCTATTACTTTCTGTGTCCATTTTTCATTAACCGAGCTGT (FRAG 992) (SEQ. ID NO: 1002)  
 BTTTGTCTCTCTBTTBCTTTCTGTGTCCBTTTTCBTTBCCGCGCTGT (FRAG 993) (SEQ. ID NO: 1003)

### Human Fc- $\xi$ Receptor CD23 Antigen (IgE Receptor)

#### Antisense Oligonucleotide Fragments

- 5'-GCC TGT GTC TGT CCT CCT GCT TCG TTC CTC TCG TTC CTG CTT GGT GCC CTT GCC G GTC CTG CTC CTC CGG GCT  
 50 GTG G GTC GTG GCC CTG GCT CCG GCT GGT GGG CTC CCC TGG CCT TCG CTG GCT GGC GGC GTG C GGG TCT TGC  
 TCT GGG CCT GGC TGT GGC CGT GGT TGG GGG TCT TC GCT GCC TCC GTT TGG GTG GC TCT CTG AAT ATT GAC CTT  
 CCT CCA TGG CGG TCC TGC TTG GAT TCT CCC GA TCT CTG BBT BTT GBC CTT CCT CCB TGG CGG TCC TGC TTG GBT  
 TCT CCC GB-3' (FRAG 1685) (SEQ. ID NO: 1696)  
 5'-GT CCT CCT-3' (FRAG 1686) (SEQ. ID NO: 1697)  
 5'-TGT GTC TGT CCT CC-3' (FRAG 1687) (SEQ. ID NO: 1698)  
 5'-GTG GCC CTG GC-3' (FRAG 1688) (SEQ. ID NO: 1699)  
 5'-CGT GGT TGG GG-3' (FRAG 1689) (SEQ. ID NO: 1700)  
 5'-TCT CTG BBT BTT GBC C-3' (FRAG 1690) (SEQ. ID NO: 1701)  
 5'-GCC TGT GTC TGT CCT CCT-3' (FRAG 994) (SEQ. ID NO: 1004)

- 5'-GCT TCG TTC CTC TCG TTC-3' (FRAG 995) (SEQ. ID NO:1005)  
 5'-CTG CTT GGT GCC CTT GCC G-3' (FRAG 996) (SEQ. ID NO: 1006)  
 5'-GTC CTG CTC CTC CGG GCT GTG G-3' (FRAG 997) (SEQ. ID NO: 1007)  
 5'-GTC GTG GCC CTG GCT CCG GCT GGT GGG CTC CCC TGG-3' (FRAG 998) (SEQ. ID NO: 1008)  
 5'-CCT TCG CTG GCT GGC GGC GTG C-3' (FRAG 999) (SEQ. ID NO: 1009)  
 5'-GGG TCT TGC TCT GGG CCT GGC TGT-3' (FRAG 1000) (SEQ. ID NO:1010)  
 5'-GGC CGT GGT TGG GGG TCT TC-3' (FRAG 1001) (SEQ. ID NO: 1011)  
 5'-GCT GCC TCC GTT TGG GTG GC (FRAG 1002) (SEQ. ID NO: 1012)  
 5'-TCT CTG AAT ATT GAC CTT CCT CCA TGG CGG TCC TGC TTG GAT TCT CCC GA (FRAG 1003) (SEQ. ID NO: 1013)  
 5'-TCT CTG BBT BTT GBC CTT CCT CCB TGG CGG TCC TGC TTG GBT TCT CCC GB (FRAG 1004) (SEQ. ID NO: 1014)

### **Human IgE Receptor $\alpha$ Subunit Anti-sense Oligonucleotide Fragments**

- 5'-GCC TTT CCT GGT TCT CTT GTT GTT TTT GGG GTT TGG CTT ACA GTA GAG TAG GGG ATT CCA TGG CAG GAG CCA  
 TCT TCT TCA TGG ACT CC TTC AAG GAG ACC TTA GGT TTC TGA GGG ACT GCT AAC ACG CCA TCT GGA GC BCB GTB  
 GBG TBG GGG BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTG GGT TTC TGB GGG BCT  
 GCT BBC BCG CCB TCT GGB GC GTT GTT TTT GGG GTT TGG CTT GCC TTT CCT GGT TCT CTT BCB GTB GBG TBG GGG  
 BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTG GGT TTC TGB GGG BCT GCT BBC BCG  
 CCB TCT GGB GC-3' (FRAG. NO: 1691) (SEQ. ID NO:1702)  
 5'-TGG BCT CC -3' (FRAG. NO: 1692) (SEQ. ID NO:1703)  
 5'-CCB TCT GGB-3' (FRAG. NO: 1693) (SEQ. ID NO:1704)  
 5'-CT GCT BBC BCG-3' (FRAG. NO: 1694) (SEQ. ID NO:1705)  
 5'-GTT TTT GGG GTT TG-3' (FRAG. NO: 1695) (SEQ. ID NO:1706)  
 5'-GCC TTT CCT GGT TCT CTT GTT GTT TTT GGG GTT TGG CTT-3' (FRAG. NO:1005) (SEQ. ID NO:1015)  
 5'-ACAGTAGAGTAGGGGATTCATGGCAGGAGCCATCTTCTTCATGGACTCC-3' (FRAG. NO:1006) (SEQ. ID NO:1016)  
 5'-TTC AAG GAG ACC TTA GGT TTC TGA GGG ACT GCT AAC ACG CCA TCT GGA GC-3' (FRAG. NO:1007) (SEQ. ID  
 NO:1017)  
 5'-BCB GTB GBG TBG GGG BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTG GGT TTC TGB  
 GGG-3' (FRAG. NO:1008) (SEQ. ID NO:1018)  
 5'-BCT GCT BBC BCG CCB TCT GGB GC-3' (FRAG. NO:1009) (SEQ. ID NO:1019)  
 5'-GTT GTT TTT GGG GTT TGG CTT-3' (FRAG. NO:1010) (SEQ. ID NO:1020)  
 5'-GCC TTT CCT GGT TCT CTT-3' (FRAG. NO:1011) (SEQ. ID NO:1021)  
 5'-BCBGTBGBGTGGGGBTTCBTTGGCBGGGCCBCTCTTCTTCTBTTGGCTCC-3' (FRAG. NO:1012) (SEQ. ID NO:1022)  
 5'-TTC BBG GBG BCC TTG GGT TTC TGB GGG BCT GCT BBC BCG CCB TCT GGB GC-3' (FRAG. NO:1013) (SEQ. ID  
 NO>1023)

### **Human IgE Receptor (Fc Epsilon R) Anti-sense Oligonucleotide Fragments**

- 5'-GCC TGT GTC TGT CCT CCT GCT TCG TTC CTC TCG TTC CTG CTT GGT GCC CTT GCC G GTC CTG CTC CGG GCT  
 GTG G GTC CTC GCC CTG GCT CCG GCT GGT GGG CTC CCC TGG CCT TCG CTG GCT GGC GGC GTG C CCC BGB BCG BGB  
 CCC GGB CCG BCB GGC CGT GGT TGG GGG TCT TC GCT GCC TCC GTT TGG GTG GC GAT CTC TGA ATA TTGA CCT TCC  
 ATG GCG GTC CTG CTT GGA GBT CTC TGB BTB TTGB CCT TCC BTG GCG GTC CTG CTT GGB-3' (FRAG: 1696) (SEQ. ID  
 NO:1707)  
 5'-TCG TTC CTC TCG-3' (FRAG: 1697) (SEQ. ID NO:1708)  
 5'-BGB BCG BGB C-3' (FRAG: 1698) (SEQ. ID NO:1709)  
 5'-TGB BTB TTGB-3' (FRAG: 1699) (SEQ. ID NO:1710)  
 5'-GCC TGT GTC TGT CCT CCT-3' (FRAG. NO:1014) (SEQ. ID NO:1024)  
 5'-GCT TCG TTC CTC TCG TTC-3' (FRAG. NO:1015) (SEQ. ID NO:1025)  
 5'-CTG CTT GGT GCC CTT GCC G-3' (FRAG. NO:1016) (SEQ. ID NO:1026)  
 5'-GTC CTG CTC CTC CGG GCT GTG G-3' (FRAG. NO:1017) (SEQ. ID NO:1027)  
 5'-GTC CTC GCC CTG GCT CCG GCT GGT GGG CTC CCC TGG-3' (FRAG. NO:1018) (SEQ. ID NO:1028)  
 5'-CCT TCG CTG GCT GGC GGC GTG C-3' (FRAG. NO:1019) (SEQ. ID NO:1029)  
 5'-CCC BGB BCG BGB CCC GGB CCG BCB-3' (FRAG. NO:1020) (SEQ. ID NO:1030)  
 5'-GGC CGT GGT TGG GGG TCT TC-3' (FRAG. NO:1021) (SEQ. ID NO:1031)  
 5'-GCT GCC TCC GTT TGG GTG GC-3' (FRAG. NO:1022) (SEQ. ID NO:1032)  
 5'-GBT CTC TGB BTB TTGB CCT TCC BTG GCG GTC CTG CTT GGB-3' (FRAG. NO:1023) (SEQ. ID NO:1033)

### **Human Histidine Decarboxylase Anti-sense Oligonucleotide Fragments**

- 5'-TCT CCC TTG GGC TCT GGC TCC TTC TC TCT CTC TCC CTC TCT CTC TGT CGC CTC CGC CTT GGC TGC TGG GGT  
 GGT GGT GC TTT TGT TCT TCC TTG CTG CC GCC CCG CTG CTT GTC T TC CTC G CTC TGT CCC TCT CTC TCT GTB CTC  
 CTC BGG CTC CBT CBT CTC CCT TGG GC-3' (FRAG. NO:1700) (SEQ. ID NO:1711)

- 5'-GGC TCT GGC (FRAG. NO:1701) (SEQ. ID NO: 1712)  
 5'-CCC TTG G (FRAG. NO:1702) (SEQ. ID NO: 1713)  
 5'-TT TGT TCT TCC (FRAG. NO:1703) (SEQ. ID NO: 1714)  
 5'-TCT CCC TTG GGC TCT GGC TCC TTC TC-3' (FRAG. NO:1024) (SEQ. ID NO: 1034)  
 5'-TCT CTC TCC CTC TCT CTC TGT -3' (FRAG. NO:1025) (SEQ. ID NO:1035)  
 5'-CGC CTC CGC CCT GGC TGC TGG GGT GGT GC-3' (FRAG. NO:1026) (SEQ. ID NO:1036)  
 5'-TTT TGT TCT TCC TTG CTG CC-3' (FRAG. NO:1027) (SEQ. ID NO:1037)  
 5'-GCC CCG CTG CTT GTC T TC CTC G-3' (FRAG. NO:1028) (SEQ. ID NO:1038)  
 5'-CTC TGT CCC TCT CTC TCT GTB CTC CTC BGG CTC CBT CBT CTC CCT TGG GC (FRAG. NO:1029) (SEQ. ID NO:1039)

#### 10 Human Beta Tryptase Anti-sense Oligonucleotide Fragments

- 5'-CTT GCT CCT GGG GGC CTC CTG GTC CCT CCG GGT GTT CCC GGC GGG CCT GGC CTG GGG CBG GGG CCG CGT BGG  
 CGC GGC TCG CCB GGB CGG GCB GCG CCB GCB GCB GCB GBT TCB GCB TCC TGG-3' (FRAG. NO:1704) (SEQ. ID NO:  
 1715)  
 5'-GCT CCT GGG GGC CT-3' (FRAG. NO:1705) (SEQ. ID NO: 1716)  
 5'-CGT BGG CGC-3' (FRAG. NO:1706) (SEQ. ID NO: 1717)  
 5'-T GGC CTG GGG-3' (FRAG. NO:1707) (SEQ. ID NO: 1718)  
 5'-CTT GCT CCT GGG GGC CTC CTG-3' (FRAG. NO:1030) (SEQ. ID NO:1040)  
 5'-GTC CCT CCG GGT GTT CCC GGC-3' (FRAG. NO:1031) (SEQ. ID NO:1041)  
 5'-GGG CCT GGC CTG GGG CBG GGG CCG CGT BGG CGC GGC TCG CCB GGB CGG GCB GCG CCB GCB GCB GCB GBT TCB  
 GCB TCC TGG-3' (FRAG. NO:1032) (SEQ. ID NO:1042)

#### Human Tryptase-I Anti-sense Oligonucleotide Fragments

- 5'-CTT GCT CCT GGG GGC CTC CTG GTC CCT CTG GCT G TT CCC GGC CCT GGB CTG GGG CBG GGG CCG CGT BGG CGC  
 GGC TCG CCB GGB CGG GCB GCG CCB GCB GCB GCB GGC TCB GCB TCC TGG CCB CGG BBT TCC-3' (FRAG. NO: 1708)  
 (SEQ. ID NO:1719)  
 5'-CT CCT GGG GGC CTC CTG-3' (FRAG. NO:1709) (SEQ. ID NO:1720)  
 5'-B TCC TGG CCB CGG BBT TCC -3' (FRAG. NO:1710) (SEQ. ID NO:1721)  
 5'-GTC CCT C-3' (FRAG. NO:1711) (SEQ. ID NO:1722)  
 5'-CTT GCT CCT GGG GGC CTC CTG-3' (FRAG. NO:1033) (SEQ. ID NO:1043)  
 5'-GTC CCT CTG GCT G TT CCC GGC-3' (FRAG. NO:1034) (SEQ. ID NO:1044)  
 5'-CCT GGB CTG GGG CBG GGG CCG CGT BGG CGC GGC TCG CCB GGB CGG GCB GCG CCB GCB GCB GCB GGC TCB GCB  
 TCC TGG CCB CGG BBT TCC -3' (FRAG. NO:1035) (SEQ. ID NO:1045)

#### Human Prostaglandin D Synthase Anti-sense Oligonucleotide Fragments

- 5'-GGT GTG CGG GGC CTG GTG CC CCT GGG CCT CGG GTG CTG CCT GT GCG CTG CCT TCT TCT CCT GG GTC CTC GCC  
 GGG GCC CTT GCT GCC CTG GCT GT GCC CTG GGG GTC TGG GTT CGG CTG T CCC CBG CBG GBC CBG TCC CBT CCB  
 CBG CGT GTG BTG BGT BGC CBT TCT CCT GCB GCC GBG-3' (FRAG. NO:1712) (SEQ. ID NO:1723)  
 5'-T TCT CCT GCB GCC GBG -3' (FRAG. NO:1713) (SEQ. ID NO:1724)  
 5'-CTT GCT GCC CTG GCT GT-3' (FRAG. NO:1714) (SEQ. ID NO:1725)  
 5'-TCT TCT CCT GG-3' (FRAG. NO:1715) (SEQ. ID NO:1726)  
 5'-GGT GTG CGG GGC CTG GTG CC-3' (FRAG. NO:1036) (SEQ. ID NO:1046)  
 5'-CCT GGG CCT CGG GTG CTG CCT GT-3' (FRAG. NO:1037) (SEQ. ID NO:1047)  
 5'-GCG CTG CCT TCT TCT CCT GG-3' (FRAG. NO:1038) (SEQ. ID NO:1048)  
 5'-GTC CTC GCC GGG GCC CTT GCT GCC CTG GCT GT-3' (FRAG. NO:1039) (SEQ. ID NO:1049)  
 5'-GCC CTG GGG GTC TGG GTT CGG CTG T-3' (FRAG. NO:1040) (SEQ. ID NO:1050)  
 5'-CCC CBG CBG GBC CBG TCC CBT CCB CBG CGT GTG BTG BGT BGC CBT TCT CCT GCB GCC GBG -3'  
 (FRAG. NO:1041) (SEQ. ID NO:1051)

#### Human Cyclooxygenase-2 Anti-sense Oligonucleotide Fragments

- 5'-GGG CGC GGG CGB GCB TCG C TTT GGG CTT TTC TCC TTT GGT T TGB GCG CCB GGB CCG CGC BCB GCB GCB GGG  
 CGC GGG CGB GCB TCG CBG CGG CGG GCB GGG-3' (FRAG. NO: 1716) (SEQ. ID NO:1727)  
 5'-G GCB GGG -3' (FRAG. NO: 1717) (SEQ. ID NO: 1728)  
 5'-TCC TTT GGT T-3' (FRAG. NO:1718) (SEQ. ID NO:1729)  
 5'-GGG CGC GGG CGB GCB TCG C-3' (FRAG. NO:1042) (SEQ. ID NO:1052)  
 5'-TTT GGG CTT TTC TCC TTT GGT T-3' (FRAG. NO:1043) (SEQ. ID NO:1053)  
 5'-TGB GCG CCB GGB CCG CGC BCB GCB GCB GGG CGC GGG CGB GCB TCG CBG CGG CGG GCB GGG -3'  
 (FRAG. NO:1044) (SEQ. ID NO:1054)

#### 55 Human Eosinophil Cationic Protein Anti-sense Oligonucleotide Fragments

- 5'-CCT CCT TCC TGG TCT GTC TGC CBG BCB BBT TTG GGB BGT GBB CBG TTT TGG BBC CBT GTT TCC CBG TCT CTG BGC TGT GGC-3' (FRAG. NO: 1719) (SEQ. ID NO: 1730)  
 5'-TTC TCC TTT GGT T-3' (FRAG. NO:1720) (SEQ. ID NO: 1731)  
 5'-T TTC TCC TTT GGT T-3' (FRAG. NO:1721) (SEQ. ID NO:1732)  
 5 5'- GGG CGC GGG CGB GCB TCG C-3' (FRAG. NO:1042) (SEQ. ID NO:1052)  
 5'- TTT GGG CTT TTC TCC TTT GGT T-3' (FRAG. NO:1043) (SEQ. ID NO:1053)  
 5'-TGB GCG CCB GGB CCG CGC BCB GCB GCB GGG CGC GGG CGB GCB TCG CBG CGG CGG GCB GGG -3' (FRAG. NO:1044) (SEQ. ID NO:1054)

### Human Eosinophil Derived Neurotoxin Anti-sense Oligonucleotide Fragments

- 10 5'-GCC CTG CTG CTC TTT CTG CT TCC CTT GGT GGG TTG GGC C GCT GGT TGT TCT GGG GTT C TTG CTG CCC CTT CTG TCC C TGT TTG CTG GTG TCT GCG C 5'- CCC CBB CBG BBG BBG CBG BCB BBT TTG GGB BGT GBB CBG TTT TGG BBC CBT GTT TCC TGT-3' (FRAG. NO: 1722) (SEQ. ID NO: 1733)  
 5'-TTC CTG T-3' (FRAG. NO:1723) (SEQ. ID NO: 1734)  
 15 5'-CTC TTT CTG CT-3' (FRAG. NO: 1724) (SEQ. ID NO:1735)  
 5'-CCC CTT CTG TCC C-3' (FRAG. NO:1725) (SEQ. ID NO: 1736)  
 5'-GCC CTG CTG CTC TTT CTG CT-3' (FRAG. NO:1047) (SEQ. ID NO:1057)  
 5'-TCC CTT GGT GGG TTG GGC C-3' (FRAG. NO:1048) (SEQ. ID NO:1058)  
 5'-GCT GGT TGT TCT GGG GTT C-3' (FRAG. NO:1049) (SEQ. ID NO:1059)  
 20 5'-TTG CTG CCC CTT CTG TCC C-3' (FRAG. NO:1050) (SEQ. ID NO:1060)  
 5'-TGT TTG CTG GTG TCT GCG C -3' (FRAG. NO:1051) (SEQ. ID NO:1061)  
 5'-CCC CBB CBG BBG BBG CBG BCB BBT TTG GGB BGT GBB CBG TTT TGG BBC CBT GTT TCC TGT-3' (FRAG. NO:1052) (SEQ. ID NO:1062)

### Human Eosinophil Peroxidase Anti-sense Oligonucleotide Fragments

- 25 5'-GCG CTC GGC CTG GTC CCG G GGG TCT CCT CTT GTT GTT GC TTG CGC CTC CTG CTG GGG GT CC CTC TGT TCT TGT TTT GGG GGC GGG CCC GGC CGT TGT CTT G GTT TGG GGG TTT CCG TTG GGG TTC TCC TGG CCC GGG CCT TGC CC GGC CGT GGT CCC GGC TTC GTTCCT GTC TCC GTC TCG GCT CTT CTG GGG CCT TGC GCT GTC TTT GGT G 5'-GCB CCG TCC BGT GBT GGT GCG GTB CTT GTC GCT GCB GCG CTC GGC CTG GTC CCG GBG BGC -3' (FRAG. NO: 1726) (SEQ. ID NO: 1737)  
 30 5'-TC GGC CTG GTC CCG G-3' (FRAG. NO: 1727) (SEQ. ID NO:1738)  
 5'-TGG GGG TTT CCG TTG-3' (FRAG. NO: 1728) (SEQ. ID NO: 1739)  
 5'-TG GTC CCG GBG BGC -3' (FRAG. NO: 1729) (SEQ. ID NO: 1740)  
 5'-GCG CTC GGC CTG GTC CCG G-3' (FRAG. NO:1053) (SEQ. ID NO:1063)  
 5'-GGG TCT CCT CTT GTT GTT GC-3' (FRAG. NO:1054) (SEQ. ID NO:1064)  
 35 5'-TTG CGC CTC CTG CTG GGG GT CC-3' (FRAG. NO:1055) (SEQ. ID NO:1065)  
 5'-CTC TGT TCT TGT TTT GGG GGC-3' (FRAG. NO:1056) (SEQ. ID NO:1066)  
 5'-GGG CCC GGC CGT TGT CTT G-3' (FRAG. NO:1057) (SEQ. ID NO:1067)  
 5'-GTT TGG GGG TTT CCG TTG-3' (FRAG. NO:1058) (SEQ. ID NO:1068)  
 5'-GGG TTC TCC TGG CCC GGG CCT TGC CC-3' (FRAG. NO:1059) (SEQ. ID NO:1069)  
 40 5'-GGC CGT GGT CCC GGC TTC GTT GC-3' (FRAG. NO:1060) (SEQ. ID NO:1070)  
 5'-CCT GTC TCC GTC TCG GCT CTT CTG-3' (FRAG. NO:1061) (SEQ. ID NO:1071)  
 5'-GGG CCT TGC GCT GTC TTT GGT G-3' (FRAG. NO:1062) (SEQ. ID NO:1072)  
 5'-GCB CCG TCC BGT GBT GGT GCG GTB CTT GTC GCT GCB GCG CTC GGC CTG GTC CCG GBG BGC -3' (FRAG. NO:1063) (SEQ. ID NO:1073)

### Human Intercellular Adhesion Molecule-1 (ICAM-1) Anti-sense Oligonucleotide Fragments

- 5'-GCG CGG GCC GGG GGC TGC TGG G GGT TGG CCC GGG GTG CCC C GCC GCT GGG TGC CCT CGT CCT CTG CGG TC GTG TCT CCT GGC TCT GGT TCC CC GCT GCG CCC GTT GTC CTC TGG GGT GGC CTT C GCT CCC GGG TCT GGT TCT TGT GT TGG GGG TCC CTT TTT GGG CCT GTT GT GGC GTG GCT TGT GTG TTC GGT TTC TGC CCT GTC CTC CGG CGT CCC CGG BGC CTC CCC GGG GCB GGB TGB CTT TTG BGG GGG BCB CBG BTG TCT GGG CBT TGC CBG GTC CTG GGB BCB GBG CCC CGB GCB GGB CCB GGB GTG CGG GCB GCG CGG GCC GGG GGC TGC TGG GBG CCB TBG CGB GGC TGB G-3' (FRAG. NO: 1730) (SEQ. ID NO: 1741)  
 5'-GGG GGC TGC TGG G-3' (FRAG. NO: 1731) (SEQ. ID NO:1742)  
 55 5'-T GTC CTC CGG CGT CCC-3' (FRAG. NO:1732) (SEQ. ID NO:1743)  
 5'-G CCB TBG CGB GGC TGB G-3' (FRAG. NO: 1733) (SEQ. ID NO: 1744)  
 5'-CTC TGG GGT GGC CTT C-3' (FRAG. NO:1734) (SEQ. ID NO:1745)  
 5'-GCG CGG GCC GGG GGC TGC TGG G-3' (FRAG. NO:1064) (SEQ. ID NO:1074)

- 5'-GGT TGG CCC GGG GTG CCC C-3' (FRAG. NO:1065) (SEQ. ID NO:1075)  
 5'-GCC GCT GGG TGC CCT CGT CCT CTG CGG TC-3' (FRAG. NO:1066) (SEQ. ID NO:1076)  
 5'-GTG TCT CCT GGC TCT GGT TCC CC-3' (FRAG. NO:1067) (SEQ. ID NO:1077)  
 5'-GCT GCG CCC GTT GTC CTC TGG GGT GGC CTT C-3' (FRAG. NO:1068) (SEQ. ID NO:1078)  
 5'-GCT CCC GGG TCT GGT TCT TGT GT-3' (FRAG. NO:1069) (SEQ. ID NO:1079)  
 5'-TGG GGG TCC CTT TTT GGG CCT GTT GT-3' (FRAG. NO:1070) (SEQ. ID NO:1080)  
 5'-GGC GTG GCT TGT GTG TTC GGT TTC-3' (FRAG. NO:1071) (SEQ. ID NO:1081)  
 5'-TGC CCT GTC CTC CGG CGT CCC-3' (FRAG. NO:1072) (SEQ. ID NO:1082)  
 5'-CGG BGC CTC CCC GGG GCB GGB TGB CTT TTG BGG GGG BCB CBG BTG TCT GGG CBT TGC CBG GTC CTG GGB BCB  
 GBG CCC CGB GCB GGB CCB GGB GTG CGG GCB GCG CGG GCC GGG GGC TGC TGG GBG CCB TBG CGB GGC TGB G-3'  
 (FRAG. NO:1073) (SEQ. ID NO:1083)

### Human Vascular Cell Adhesion Molecule 1 (VCAM-1) Anti-sense Oligonucleotide Fragments

- 5'-CCT CTT TTC TGT TTT TCC C CTC TGC CTT TGT TTG GGT TCG CTT CCT TTC TGC TTC TTC C CTG TGT CTC CTG TCT  
 CCG CTT TTT TCT TC GTC TTT GTT GTT TTC TCT TCC TTG CTG BGC BBG BTB TCT BGB TTC TGG GGT GGT CTC GBT  
 TTT BBBB GCT TGB GBB GCT GCB BBC BTT BTC CBB BGT BTB TTT GBG GCT CCB BGG BTC BCG BCC BTC TTC CCB GGC  
 BTT TTB BGT TGC TGT CGT-3' (FRAG. NO: 1735) (SEQ. ID NO: 1746)  
 5'-C TGT CGT-3' (FRAG. NO:1736) (SEQ. ID NO:1747)  
 5'-TGC TTC TTC C-3' (FRAG. NO:1737) (SEQ. ID NO:1748)  
 HSVCAM1AS1: 5'-CCT CTT TTC TGT TTT TCC C-3' (FRAG. NO:1074) (SEQ. ID NO:1084)  
 HSVCAM1AS2: 5'-CTC TGC CTT TGT TTG GGT TCG-3' (FRAG. NO:1075) (SEQ. ID NO:1085)  
 HSVCAM1AS3: 5'-CTT CCT TTC TGC TTC TTC C-3' (FRAG. NO:1076) (SEQ. ID NO:1086)  
 HSVCAM1AS4: 5'-CTG TGT CTC CTG TCT CCG CTT TTT TCT TC-3' (FRAG. NO:1077) (SEQ. ID NO:1087)  
 HSVCAM1AS5: 5'-GTC TTT GTT GTT TTC TCT TCC TTG-3' (FRAG. NO:1078) (SEQ. ID NO:1088)  
 CTG BGC BBG BTB TCT BGB TTC TGG GGT GGT CTC GBT TTT BBBB GCT TGB GBB GCT GCB BBC BTT BTC CBB BGT BTB  
 TTT GBG GCT CCB BGG BTC BCG BCC BTC TTC CCB GGC BTT TTB BGT TGC TGT CGT (FRAG. NO:1079) (SEQ. ID NO:1089)

### Human Endothelial Leukocyte Adhesion Molecule (ELAM-1) Anti-sense Oligonucleotide Fragments

- 5'-BBG TGB GBG CTG BGB GBB BCT GTG BBG CBB TCB TGB CTT CBB GBG TTC TTT TCB CCC GTT CTT GGC TTC TTC TGT  
 C CGT TGG CTT CTC GTT GTC CC TGT GGG CTT CTC GTT GTC CC CCC TTC GGG GGC TGG TGG GGC CGT CCT TGC CTG  
 CTG G GTT CTT GGC TTC TGT CCG T TGG CTT CTC GTT GTC CC TGT GGG CTT CTC GTT GTC CC CCC TTC GGG  
 GGC TGG TGG GGC CGT CCT TGC CTG CTG G (FRAG. NO: 1738) (SEQ. ID NO: 1749)  
 5'-CCT TGC CTG CTG G-3' (FRAG. NO: 1739) (SEQ. ID NO: 1750)  
 5'-GTT GTC CC-3' (FRAG. NO: 1740) (SEQ. ID NO:1751)  
 5'-GTT CTT GGC TTC TTC TGT C-3' (FRAG. NO:1080) (SEQ. ID NO:1090)  
 5'-GGC TGG TGG-3' (FRAG. NO:1083) (SEQ. ID NO:1093)  
 5'-CGT TGG CTT CTC GTT GTC CC-3' (FRAG. NO:1081) (SEQ. ID NO:1091)  
 5'-TGT GGG CTT CTC GTT GTC CC-3' (FRAG. NO:1082) (SEQ. ID NO:1092)  
 5'-CCC TTC GGG GGC TGG TGG-3' (FRAG. NO:1083) (SEQ. ID NO:1093)  
 5'-GGC CGT CCT TGC CTG CTG G-3' (FRAG. NO:1084) (SEQ. ID NO:1094)

### Human P Selectin Fragments

- 5'-TTT TCT CTT TCG CTT TCT TTT CGT CTC CTG TTC CTC CTT TT TTG CTG TTT TTT CTC CTT CTT CTC TCC TTT  
 CTT TTC-3' (FRAG. NO: 1741) (SEQ. ID NO: 1752)  
 5'-TCC TTT CTT TTC-3' (FRAG. NO: 1742) (SEQ. ID NO: 1753)  
 5'-CTC CTT TT-3' (FRAG. NO:1743) (SEQ. ID NO:1754)  
 5'-TTT TCT CTT TCG CTT TCT TTT CGT CTC CTG TTC CTC CTT TT-3' (FRAG. NO:1085) (SEQ. ID NO:1095)  
 5'-TTG CTG TTT TTT CTC CTT CTT CTC TCC TTT CTT TTC-3' (FRAG. NO:1086) (SEQ. ID NO:1096)

### Human Endothelial Monocyte Activating Factor Anti-sense Oligonucleotide Fragments

- 5'-TTT TCT CTT TCG CTT TCT TTT CGT CTC CTG TTC CTC CTT TT TTG CTG TTT TTT CTC CTT CTT CTC TCC TTT  
 CTT TTC-3' (FRAG. NO: 1744) (SEQ. ID NO: 1755)  
 5'-CC TTT CTT TTC (FRAG. NO: 1745) (SEQ. ID NO: 1756)  
 5'-CTG TTC CTC CTT TT-3' (FRAG. NO:1746) (SEQ. ID NO:1757)  
 5'-TTT TCT CTT TCG CTT TCT TTT CGT CTC CTG TTC CTC CTT TT-3' (FRAG. NO:1087) (SEQ. ID NO:1097)  
 5'-TTG CTG TTT TTT CTC CTT CTT CTC TCC TTT CTT TTC-3' (FRAG. NO:1088) (SEQ. ID NO:1098)

**Human IL3\* Anti-sense Oligonucleotide Fragments**

- 5'-CTC TGT CTT GTT CTG GTC CTT CGT GGG GCT CTG TGT CGC GTG G GTG CGG CCG TGG CC GGC GGB CCB GGB GTT  
GGB GCB GGB GCB GGB CGG GCB GGC GGC TCB TGT TTG GBT CGG CBG GBG GCB CTC (FRAG. NO: 1747) (SEQ. ID NO:  
1758)
- 5'-G GBG GCB CTC-3' (FRAG. NO: 1748) (SEQ. ID NO: 1759)
- 5'-GT GGG GCT CTG-3' (FRAG. NO: 1749) (SEQ. ID NO: 1760)
- HUMIL3AAS1: 5'-CTC TGT CTT GTT CTG GTC CTT CGT GGG GCT CTG-3' (FRAG. NO: 1089) (SEQ. ID NO: 1099)
- HUMIL3AAS2: 5'-TGT CGC GTG G GTG CGG CCG TGG CC-3' (FRAG. NO: 1090) (SEQ. ID NO: 1100)
- GGC GGB CCB GGB GTT GGB GCB GGB GCB GGB CGG GCB GGC GGC TCB TGT TTG GBT CGG CBG GBG GCB CTC (FRAG.  
NO: 1091) (SEQ. ID NO: 1101)

**Human IL3 Receptor Anti-sense Oligonucleotide Fragments**

- 5'-TCT GGG GTG TCC TGG CCT TCG TGG TTC CTC TTT CGT TTG CCG TCC GCG GGG GCC CCC GGG CCT GGC TGC  
GCT CCT GCC CCG CCT CTT TCC CGG GCT CTT GCG CTG GGG GGT GCT CC CGT GTG TTT GCG CCC TC CTC CTG GTC  
CGG CTT GTC GTT TTG GGG CCG GCT TTG CCC GCC TCC CGG CGC CTG GCC CGG CC TTC CTG GGC TGC GTG CGC GTT  
CTG TTC TTC CTC GCT CTG GGG TGT CCT GGC CTT CGT GGT TCC TCT TCC TTC GTT TGC CGT CCG CGG GGG CCC  
CCG GGC CT GGC TGC GCT CCT GCC CCG CCT CTT TCC CGG GCT CTT GCG CTG GGG GGT GCT CCC GTG TGT TTG CGC  
CCT CCT CCT GGT CGC GCT TGT CGT TTT GG GGC CGG CTT TGC CCG CCT CCC GGC GCC TGG CCC GGC CTT CCT GGG  
CTG CGT GCG CGT TCT GTT CTT CTT CCT GGC GCA GGA GAC AGG GCA GGG CGA TCA GGA GCA GCG TGA GCC AAA  
GGA GGA CCA TCG GGA ACG CAG CTC CGG AAC GCA GGA CAG AGG TGC C GC BGG BGB CBG GGC BGG CCG BTC BGG  
BGC BGC GTG BGC CBB BGG BCC BTC GGG BBC GCB GCT CCG GBB CGC BGG BCB GBG GTG CC-3' (FRAG. NO: 1750)  
(SEQ. ID NO: 1761)
- GBG GTG CC-3' (FRAG. NO: 1751) (SEQ. ID NO: 1762)
- 5'-GCC CCG C-3' (FRAG. NO: 1752) (SEQ. ID NO: 1763)
- 5'-TCTGGGGTGTCTG (FRAG. NO: 1092) (SEQ. ID NO: 1102)
- 5'-GCCTTCGTGGTTCC (FRAG. NO: 1093) (SEQ. ID NO: 1103)
- 5'-TCTTCCTTCGTTTGC (FRAG. NO: 1094) (SEQ. ID NO: 1104)
- 5'-CGTCCGCGGGGGCCCCGGGCT (FRAG. NO: 1095) (SEQ. ID NO: 1105)
- 5'-GGC TGC GCT CCT GCC CCG C (FRAG. NO: 1096) (SEQ. ID NO: 1106)
- 5'-CTCTTTCCCGGGCTCTT (FRAG. NO: 1097) (SEQ. ID NO: 1107)
- 5'-GCGCTGGGGGGTGCTCC (FRAG. NO: 1098) (SEQ. ID NO: 1108)
- 5'-CGTGTGTTTGGCGCCCTCCTCTGGTCGC (FRAG. NO: 1099) (SEQ. ID NO: 1109)
- 5'-GCTGTGCTTTTGG (FRAG. NO: 1100) (SEQ. ID NO: 1110)
- 5'-GGCCGGCTTTGGCCGCTCCC (FRAG. NO: 1101) (SEQ. ID NO: 1111)
- 5'-GGCGCCTGGCCCGGCC (FRAG. NO: 1102) (SEQ. ID NO: 1112)
- 5'-TTCCTGGGCTGCGTGGCGC (FRAG. NO: 1103) (SEQ. ID NO: 1113)
- 5'-GTTCTGTTCTTCTCTCTGGC (FRAG. NO: 1104) (SEQ. ID NO: 1114)
- 5'-GCB GGB GBC BGG GCB GGG GCB TCB GGB GCB GCG TGB GCC BBB GGB GGB CCB TCG GGB BCG CBG CTC CGG BBC  
GCB GGB 5'-CBG BGG TGC C (FRAG. NO: 1105) (SEQ. ID NO: 1115)

**Human IL-4 Anti-sense Oligonucleotide Fragments**

- 5'-CTC TGG TTG GCT TCC TTC GCC GGC BCB TGC TBG CBG GBB GBB CBG BGG GGG BBG CBG TTG GGB GGT GBG BCC  
CBT TBB TBG GTG TCG B-3' (FRAG. NO: 1753) (SEQ. ID NO: 1764)
- 5'-GCC GGC BCB-3' (FRAG. NO: 1754) (SEQ. ID NO: 1765)
- 5'-T TCC TTC-3' (FRAG. NO: 1755) (SEQ. ID NO: 1766)
- 5'-CTC TGG TTG GCT TCC TTC-3' (FRAG. NO: 1106) (SEQ. ID NO: 1116)
- 5'-GCCGGCBCTGCTBGCBBGGBBGBGGBGGGGBGCBGTTGGGGGTGBGCCCBTBBTBGGTGTGCB-3' (FRAG. NO: 1107)  
(SEQ. ID NO: 1117)

**Human IL4 Receptor Anti-sense Oligonucleotide Fragment**

- 5'-TCT GCC CTG TCC GCC GGC TCT TCG GTG GCT CGG CCC CGC TCC TTG TCT TGC CGC GGG TTG GTT CCT GGG CCT  
GGT TCT TGC GGG CGT TTC GGT CTG CTG GCT GGT CTG GGC CCG CGG TGC GGC GGG TGG CTT GCT GTT CTG CCT GGG  
CTC TCC CCT CTC CTC CTT TTC TCC CTT CTG TCT TGC CTC CTT CCT CTG GGT CCT CTT GGC CTG GGC GCT CTT  
CCC CTC GGG CGG CTG CGG GCG CTC GTG CTG CCT GGT CCG CTC CCT GGG GGT GCT CCT TCC CTT TCC CCG CTC GTG  
GGG TTT GCG GGG CTG GGC TGC CCT GGG GGG TCT GGG CCT TTT GGG GTC GGC TGG CTG CTT CGG GCC GCC  
TGG GCT TCC CTG TGC CCC TTT CCT CTG CTG GGT CCC CCT CCC GTT CCA AGC TGC ACC GCA CAG ACC GGC GCT ACA  
GGA CAG AGC CAG GCA AGC ACC CAT GGG GAT CCA GGC CCA GCT GTT CCB BGC TGC BCC GCB CBG BCC GGC GCT  
BCB GGB CBG BGC CBG GCB BGC BCC CBT GGG GBT CCB GGC CCB GCT G-3' (FRAG. NO: 1756) (SEQ. ID NO: 1767)
- 5'-TCTGCGC-3' (FRAG. NO: 1757) (SEQ. ID NO: 1768)
- 5'-CCT GCT CCT GGG G (FRAG. NO: 1758) (SEQ. ID NO: 1769)
- 5'-TCTGCGCGCCCTGCTCC (FRAG. NO: 1108) (SEQ. ID NO: 1118)

### Human IL5\* Anti-sense Oligonucleotide Fragments

55 Human IL-5 Receptor Anti-sense Oligonucleotide Fragments

49

### Human IL-6 Receptor Fragments

50



(FRAG. NO:1187) (SEQ. ID NO:1197)

**Human IL-6 Anti-sense Oligonucleotide Fragments**

- 5'-GGGGGTGGCT TCCTGCCGCG TCTCTGGGCC GTCCCGTCCC TCGGCCCCGC GCCGCGCTCG GCTCCTCTCC CTCTGGCCCG  
GCTCGGGGCG GGGCGGGGCG GTGGGCGGGC GGCCTGCCCT TCGCGCGGCG GCTGGCCCTT GCTGGCCGTC GGCTGCGGCG  
TGCTGGCTGC CTTGCTGGCC GCGCCGGGCG CTGTCCGCTT CTGCGGGGCG TGTCTCTTGG CTTGTCTTCC GGCTCTTCTG  
CTGGGGTGGG GCTGGGCGGC CGGCCCGGTG CTGGGGCTCC TCGGGGGGGG GGGCTCTTCC GGGCTGTCTC CCTCCGGGGC  
GGGGGTTTCT GGCCGTGGGG GTCTTGCTG GCCTCCGGGC TCTGCTTGT CTGCTTCC TTCTCTGGTC GGTGTGGCT  
CGGGGCTCCG TGGGTCCCTG GCGCCCGTTT GTGTTTTGTC TTTTCCCTG GCGTCCCTGT GCCCTCTCC TCTCTTCT  
CTGCTTCTCG CTCTCCTTG TGGGGCCCTC CTTGCTGCTC TTGGTTTTGG GCTTTTTTTC TCTCTCTCT TTTTCTGTGCG  
TGGGCTTCC GCACGCTCT TGCCACCTCC TGCGCAGGCG AGCGCTTGG GGCCAGCGCC GCTCCCGGCG CGGCCAGCAG  
GGCAGCCAGC AGCGCGCAGC CGACGGCCAG CATGCTTCTT CTTGCGCTAC CACTCCATGG TCCCGCAGAG GCGGACAGCG  
GCBGCGCTC TTGCCBCCTC CTGCGCBGGG CBGCGCTTG GGGCCBGGC CGCTCCCGCG GCGGCCBGB GGGCBGCCBG  
CBGCGCGCBG CCGBCGGCCB GCBTGCTTCC TCCTCGGCTB CCBCTCCBTG GTCCGCBGB GCGGBCBGG C-3' (FRAG.  
NO:1772) (SEQ. ID NO:1783)
- 5'-GGGCBGG-3' (FRAG. NO:1773) (SEQ. ID NO:1784)  
5'-GBBGGCBG CBGGC-3' (FRAG. NO:1774) (SEQ. ID NO:1785)  
5'-CCBGGBGBG CCCC-3' (FRAG. NO:1775) (SEQ. ID NO:1786)  
5'-BGGG BGGGGCBBC-3' (FRAG. NO:1776) (SEQ. ID NO:1787)
- 5'-GCT TCT CTT TCG TTC CCG GTG GGC TCG-3' (FRAG. NO:1188) (SEQ. ID NO:1198)  
5'-GTG GCT GTC TGT GTG GGG CGG CT-3' (FRAG. NO:1189) (SEQ. ID NO:1199)  
5'-GTG CCT CTT TGC TGC TTT C-3' (FRAG. NO:1190) (SEQ. ID NO:1200)  
5'-GAT TCT TTG CCT TTT TCT GC-3' (FRAG. NO:1191) (SEQ. ID NO:1201)  
5'-CTCCTGGGGG TBCTGGGGCB GGGBBGGCBG CBGGCBBCB CBGGCBGCG CCCBGGGBGB BGGCBCTGG BCCGBBGGCG  
CTTGGBGB BGGBTTCBT BGCTGGGCTC CTGGBGGGB GBTBGGC-3' (FRAG. NO:1777) (SEQ. ID NO:1788)

25 **Human Monocyte-derived Neutrophil Chemotactic  
Factor Anti-sense Oligonucleotide Fragments**

- 5'-GGGGTGGBBB GGTTTGGBGT BTGTCTTTBT GCBCTGBCBT CTBBGTTCTT TBGCBCTCCT TGGCBBBCT GCBCCTTCBC  
BCBGBGCTGC BGGBTBGGG BBGGCTGCCB BGGBGGCCBC GGCCBGCTTG GBBGTCTGT TTBCBCCBGB TGBGTTGGT  
CCTTCGGGC TTGTGTGCTC TGCTGTCTT TGGTTCCTC CGGTGGTTC TTCTGGCTC TTGTCTTTC TCTTGG CCCT  
TGGC-3' (FRAG. NO:1778) (SEQ. ID NO: 1789)
- 5'-GGBGT BTG-3' (FRAG. NO:1779) (SEQ. ID NO: 1790)  
5'-GCBCTGBCBT CT-3' (FRAG. NO:1780) (SEQ. ID NO:1791)  
5'-CCG GTG G-3' (FRAG. NO:1781) (SEQ. ID NO: 1792)  
5'-GG CCC TTG GC-3' (FRAG. NO:1782) (SEQ. ID NO: 1793)
- 5'-GCT TGT GTG CTC TGC TGT CTC T-3' (FRAG. NO:1192) (SEQ. ID NO:1202)  
5'-TGG TTC CTT CCG GTG GTT TCT TCC TGG CTC TTG TCC T-3' (FRAG. NO:1193) (SEQ. ID NO:1203)  
5'-TTC TCT TGG CCC TTG GC-3' (FRAG. NO:1194) (SEQ. ID NO:1204)  
5'-GGGGTGGBBB GGTTTGGBGT BTGTCTTTBT GCBCTGBCBT CTBBGTTCTT TBGCBCTCCT TGGCBBBCT GCBCCTTCBC  
BCBGBGC-3' (FRAG. NO:1783) (SEQ. ID NO: 1794)

40 **Human Neutrophil Elastase (Medullasin) Anti-sense Oligonucleotide Fragments**

- 5'-GGGCTCCCGC CGCGBGGGT TBTGGGCTCC CBGGBCBCC CGCBCCGCG GBCGTTTBC BTTCGCCBCG CBGTGCGCGG  
CCGBCBTGBC GBBGTTGGG GCBTTCBGG TGGCGCGCB GBBGTGGCTT CCGCGCBGCT GCBGGGBCB CBTGBBGGG  
CBGCGTGGG GCGCGCTCG CCGGCCCTCC BCBTCTCCG BGGCCBGC GGTGCCCCC BGCBCBGG CCGCBGGBC  
BCBGGCBGG BGCBCGCB GTCGGCGGCC GGGGTCTBT GTGGGCTGG GGTCCGGG TCTCTGCCCC TCCGTGCTGG  
TGGGGCTGG GCTCCGGG TCTTGCCCC TCCGTGCGC GTGGGCGCG GCTCGCCGCG CCCCCCTGC CGGGTGGGCT  
CCCCCGCG GCGGCTCG CCGCCCTCG TGGTCTGCTG TGGCGGGT CCGGTCCCG GGGTGGGCG CBGTGCGCG  
GCCBGGGT-3' (FRAG. NO:1784) (SEQ. ID NO: 1795)  
5'-GG TGG GGC-3' (FRAG. NO:1785) (SEQ. ID NO: 1796)  
5'-G GGG CCG -3' (FRAG. NO:1786) (SEQ. ID NO:1797)
- 5'-GGC CGG GTC CGG G-3' (FRAG. NO:1787) (SEQ. ID NO: 1798)  
5'-TGG TGG GGC TGG GGC TCC GGG GTC TCT GCC CCT CCG TGC-3' (FRAG. NO:1195) (SEQ. ID NO:1205)  
5'-CGC GTG GGG CCG CGC TCG CCG GCC CCC C-3' (FRAG. NO:1196) (SEQ. ID NO:1206)  
5'-CCT GCC GGG TGG GCT CCC GCC GCG-3' (FRAG. NO:1197) (SEQ. ID NO:1207)  
5'-CGC CGG CCT GCC GGC CCC TC-3' (FRAG. NO:1198) (SEQ. ID NO:1208)
- 5'-GTG GGT CCT GCT GGC CGG GTC CGG GTC CCG GGG GTG GGG-3' (FRAG. NO:1199) (SEQ. ID NO:1209)  
5'-CGC GBG TCG GCG GCC GBG GGT C-3' (FRAG. NO:1200) (SEQ. ID NO:1210)  
5'-GGGCTCCCGC CGCGBGGGT TBTGGGCTCC CBGGBCBCC CGCBCCGCG GBCGTTTBC BTTCGCCBCG CBGTGCGCGG

CCGBCBTGBC GBBGTTGGGC GCBBTCBGGG TGGCGCCGCB GBBGTGGCCT CCGCGCBGCT GCBGGGBCBC CBTGBBGGGC  
 CBCGCGTGGG GCCGCGCTCG CCGGCCCCC BCBBTCTCCG BGGCCBGC GC GTGCCCCC BGCBCBGG CCGCBGGGBC  
 BCBGGCBGG BGCBCGCGB GTGCGCGGCC BGGGGTCTG GTGGGGCTGG GGCTCCGGG TCTTGCCCC TCCGTGC-3'  
 (FRAG. NO:1788) (SEQ. ID NO: 1799)

### 5 Human Neutrophil Oxidase Factor Anti-sense Oligonucleotide Fragments

5'-CGGGBGTGGG GGTCTGBC GGCCTGGBG GCBTCBGGG CTCCTTCCB GTCCTTCTG TCCGCTGCCB GCBCCCCTTC  
 BTTCBGBGG CTGTTGGCTT CCBCCBGGG CBTGTTBGG TBGBBCTBG GBGGCCGGC TCCBCCBGG CBTGTTCTT  
 TCTTGCCG TGCCTCTTG GGGTTTTCG TCTGGGTGG CTTTCTCTT GGGGCTGTG CTGGGCTCTT CTTTTGTTT  
 CTGGCTGTG GCTCTCTG GCCCTTCCC TTGGGTGCT TGTITTTG GCCTCCBCCB GGBCBTG-3' (FRAG. NO:1789)

10 (SEQ. ID NO: 1800)

5'-CGGGBGTGGG GG-3' (FRAG. NO:1790) (SEQ. ID NO: 1801)

5'-GCCBGCBCCCC-3' (FRAG. NO:1791) (SEQ. ID NO: 1802)

5'-C CBC CBG-3' (FRAG. NO:1792) (SEQ. ID NO: 1803)

5'-GGC CTC CBC CBG GGB CBT G-3' (FRAG. NO:1201) (SEQ. ID NO:1211)

15 5'-GTC CTT CTT GTC CGC TGC C-3' (FRAG. NO:1202) (SEQ. ID NO:1212)

5'-TCT CTG GGG TTT TCG GTC TGG GTG G-3' (FRAG. NO:1203) (SEQ. ID NO:1213)

5'-GCT TTC CTC CTG GGG CTG CTG CTG-3' (FRAG. NO:1204) (SEQ. ID NO:1214)

5'-GGC TCT TCT TTT TGT TTC TGG CCT GGT G-3' (FRAG. NO:1205) (SEQ. ID NO:1215)

5'-CTC TCT CGT GCC CTT TCC-3' (FRAG. NO:1206) (SEQ. ID NO:1216)

20 5'-CTT GGG TGT CTT GTT TTT GT-3' (FRAG. NO:1207) (SEQ. ID NO:1217)

5'-GGC CTC CBC CBG GGB CBT G-3' (FRAG. NO:1208) (SEQ. ID NO:1218)

5'-CGGGBGTGGG GGTCTGBC GGCCTGGBG GCBTCBGGG GCBTCBGGG CTCCTTCCB GTCCTTCTG TCCGCTGCCB GCBCCCCTTC  
 BTTCBGBGG CTGTTGGCTT CCBCCBGGG CBTGTTBGG TBGBBCTBG GBGGCC-3' (FRAG. NO:1793) (SEQ. ID NO:  
 1804)

### 25 Human Cathepsin G Anti-sense Oligonucleotide Fragments

5'-CCCTCCCBT CTGCTCTGBC CTGCTGGBCT CTGGBTCTG BGBTBCGCCB TGTBGGGGCG GGBGTGGGGC CTGCTCTCCC  
 GGCCTCCGT GBTCTCCCT GCCTCBGCCC CBGTGGGTBG GBGBBBGGCC BGCBBBGC BGBGTGGCTG CBTCTTCTT  
 GGTGGGGCT GCTCTCCCG CCTCGTGTG TTGCTGGTG TTTTCCGTC TCTGGTCTG CTTCCGGGGT CGT-3' (FRAG.  
 NO:1794) (SEQ. ID NO: 1805)

30 5'-GBBGTBCGCC-3' (FRAG. NO:1795) (SEQ. ID NO: 1806)

5'-CBGCCCCBG-3' (FRAG. NO:1796) (SEQ. ID NO: 1807)

5'-TCC CGT CTC TGG-3' (FRAG. NO:1797) (SEQ. ID NO: 1808)

5'-GTG GGG CCT GCT CTC CCG GCC TCC G-3' (FRAG. NO:1209) (SEQ. ID NO:1219)

5'-TGT GTT GCT GG GTG TTT TCC CGT CTC TGG-3' (FRAG. NO:1210) (SEQ. ID NO:1220)

35 5'-TCT GCC TTC GGG GGT CGT-3' (FRAG. NO:1211) (SEQ. ID NO:1221)

5'-CCCTCCCBT CTGCTCTGBC CTGCTGGBCT CTGGBTCTG BGBTBCGCCB TGTBGGGGCG GGBGTGGGGC CTGCTCTCCC  
 GGCCTCCGT GBTCTCCCT GCCTCBGCCC CBGTGGGTBG GBGBBBGGCC BGCBBBGC BGBGTGGCTG-3' (FRAG.  
 NO:1798) (SEQ. ID NO: 1809)

### 40 Human Defensin 1 Anti-sense Oligonucleotide Fragments

5'-CCGGGGCTGC BGCBBCTCB TCBGCTCTT GCTGGBGTGG CTCBGCCTGG GCCTGCBGGG CCBCCBGGG BBTGGCBGCB  
 BGGBTGGGCB GGGTCTCTBT GGCTGGGGTC BCBGTCTCTC TBGCTBGGCB GGGTGBCCBG BGBGGGC GGG TCC TCB TGG  
 CTG GGG GCC TGG GCC TGC BGG GCC GCT CTT GCC TGG BGT GGC TC GCC CBG BGT CTT CCC TGG T-3' (FRAG. NO:1799)  
 (SEQ. ID NO: 1810)

45 5'-CCGGGGC-3' (FRAG. NO:1800) (SEQ. ID NO: 1811)

5'-GG GCCTGCBGGG CC-3' (FRAG. NO:1801) (SEQ. ID NO: 1812)

5'-GGCBGCB BGG-3' (FRAG. NO:1802) (SEQ. ID NO: 1813)

5'-GGG TCC TCB TGG CTG GGG-3' (FRAG. NO:1212) (SEQ. ID NO:1222)

5'-GCC TGG GCC TGC BGG GCC-3' (FRAG. NO:1213) (SEQ. ID NO:1223)

5'-GCT CTT GCC TGG BGT GGC TC-3' (FRAG. NO:1214) (SEQ. ID NO:1224)

50 5'-GCC CBG BGT CTT CCC TGG T-3' (FRAG. NO:1215) (SEQ. ID NO:1225)

5'-CCGGGGCTGC BGCBBCTCB TCBGCTCTT GCTGGBGTGG CTCBGCCTGG GCCTGCBGGG CCBCCBGGG BBTGGCBGCB  
 BGGBTGGGCB GGGTCTCTBT GGCTGGGGTC BCBGTCTCTC TBGCTBGGCB GGGTGBCCBG BGBGGGC-3' (FRAG. NO:1803)  
 (SEQ. ID NO: 1814)

### Human Defensin 3 Anti-sense Oligonucleotide Fragments

- 5'-CGCTGCBBTC TGCTCCGGGG CTGCBGCBBB CTCBTCBGCTC TTGCCTGGBGTG GCTCBGCCTGG GCCTGCBGGG  
CCBCCBGGGB BTGGCBGCBG GBTGGCBGGG TCCTCBTGGC TGGGGTCBCCT GGBGBGGGB GBGCBGGGG  
TCCTCBTGGC TGGGGTCCT CTCTCCCGTC CT-3' (FRAG. NO:1804) (SEQ. ID NO:1815)
- 5'-GGCBGCBGG-3' (FRAG. NO:1805) (SEQ. ID NO:1816)
- 5'-GG CTG GGG-3' (FRAG. NO:1806) (SEQ. ID NO:1817)
- 5'-GGGGTCBCC-3' (FRAG. NO:1807) (SEQ. ID NO:1818)
- 5'-GGG TCC TCB TGG CTG GGG TC-3' (FRAG. NO:1216) (SEQ. ID NO:1226)
- 5'-CCT CTC TCC CGT CCT-3' (FRAG. NO:1217) (SEQ. ID NO:1227)
- 5'-CGCTGCBBTC TGCTCCGGGG CTGCBGCBBB CTCBTCBGCTC TTGCCTGGBGTG GCTCBGCCTGG GCCTGCBGGG  
CCBCCBGGGB BTGGCBGCBG GBTGGCBGGG TCCTCBTGGC TGGGGTCBCCT GGBGBGGGB GBGCBGG-3' (FRAG.  
NO:1808) (SEQ. ID NO:1819)

### **Human Macrophage Inflammatory Protein-1-alpha/RANTES Receptor Anti-sense Oligonucleotide Fragments**

- 5'-GTCTTTGTTT CTGGGCTCGT GCCCBTCCC GGCTTCTCTC TGGTTCCGTC CTCTGTGGTG TTTGGCCCTG CTTCTTTT  
CCTGTTGAGG GGGCAGCAGT TGGGCCCAA AGGCCCTCTC GTTCACCTTC TGGCACGGAGT GCATCCCCATA  
GTCAAACCTCT GTGGTCGTGT CATAGTCCTC TGTGGTGTGT GGAGTTTCCA TCCCGGCTTC TCTCTGGTTC CAAGGGAGB  
GGGGCBGCB GTTGGGCCCC BBBGGCCCTC TCGTTCBCCT TCTGGCBGG BGTTCBCTCC CCBTGTCCB BCTCTGTGGT  
CGTGTCTBG TCCTCTGTGG TGTGTGGBT TTCCBTCCCG GCTTCTCTCT GTTCCBBGG GB-3' (FRAG. NO:1809) (SEQ.  
ID NO:1820)
- 5'-GGGCC CC-3' (FRAG. NO:1810) (SEQ. ID NO:1821)
- 5'-GGGGCBGCB-3' (FRAG. NO:1811) (SEQ. ID NO:1822)
- 5'-CCCGGCTTC-3' (FRAG. NO:1812) (SEQ. ID NO:1823)
- 5'-GTC TTT GTT TCT GGG CTC GTG CC-3' (FRAG. NO:1218) (SEQ. ID NO:1228)
- 5'-CCB TCC CGG CTT CTC TCT GGT TCC-3' (FRAG. NO:1219) (SEQ. ID NO:1229)
- 5'-GTC CTCTGT GGT GTT TGG-3' (FRAG. NO:1220) (SEQ. ID NO:1230)
- 5'-CCC TGC TTC CTT TTG CCT GTT-3' (FRAG. NO:1221) (SEQ. ID NO:1231)
- 5  
GAGGGGGCAGCAGTTGGGCCCCAAAGGCCCTCTCGTTCACCTTCTGGCACGGAGTTGCATCCCCATAGTCAAACCTCTGTGGT  
CGT-3'
- (FRAG. NO:1222) (SEQ. ID NO:1232)
- 5'-GTCATAGTCTCTGTGGTGTGTGGAGTTCCATCCCGCTTCTCTGTTTCAAGGA-3' (FRAG. NO:1223) (SEQ. ID  
NO:1233)
- 5'-GBGGGGCBG CBGTTGGGCC CBBBGGCCC TCTCGTTCBC CTTCTGGCBC GGBGTTGCBT CCCCBTBGT BBBCTCTGTG  
GTCGTG-3' (FRAG. NO:1224) (SEQ. ID NO:1234)
- 5'-TCBTGTCTCTGTGGTGTGTGGBTTCBTTCCCGCTTCTCTGTTCCBBGGGB-3' (FRAG. NO:1225) (SEQ. ID NO:1235)

### **RANTES Antisense Oligonucleotide Fragments**

- 5'-GGGCBGGGG CBGTGGGCGG GCBTGTBGG CBBGCBGCB GGGTGTGGT TCCBGGBBT BTGGGBGGC BGBTGCBGGB  
GCGCBGGBGG CBGTBGCBBT GBGGTBGCB GCBGGGCGT CCGCGGBGC CTTCTBGGTB CCTGTGGBG GGCTGTCGGB  
GGGGGTGTGG TGTCCGCTTG GCGGTTCTTT CGGGTGTTC TTCTCTGGGT TGGCCTGCTG CTCGTCGTGT CGCTCCGCTC  
CCGGTTCGT CTCGCTCTGT CGCCCTTCC TTCTGTGCTG TGTCTCTCC TTCTTGCCT CT-3' (FRAG. NO: 1813) (SEQ.  
ID NO: 1824)
- 5'-GGGTTGGC-3' (FRAG. NO: 1814) (SEQ. ID NO: 1825)
- 5'-CGGG CBG-3' (FRAG. NO: 1815) (SEQ. ID NO: 1826)
- 5'-CCCGGTTTCG-3' (FRAG. NO: 1816) (SEQ. ID NO: 1827)
- 5'-GGGTGTGGT-3' (FRAG. NO: 1817) (SEQ. ID NO: 1828)
- 5'-GGGCBGGGG CBGTGGGCGG GCBTGTBGG CBBGCBGCB GGGTGTGGT TCCBGGBBT BTGGGBGGC BGBTGCBGGB  
GCGC-3' (FRAG. NO:1226) (SEQ. ID NO:1236)
- 5'-BGBGGCBGTBGCBBTGBGGTBGCBGCGGCGTCCGCGGBGCCCTTCBTGGTBCTGTGGBGGGCTGTCGGBGG-3'  
(FRAG. NO:1227) (SEQ. ID NO:1237)
- 5'-GGGTGTGGTGTCCGCTTGGCGGTCTTTTCGGGTGTTCTTCTCTGGGTGGCCTGCTGCTCGTCGTGGTC-3' (FRAG.  
NO:1228)
- (SEQ. ID NO:1238)
- 5'-GCTCCGCTCCCGGTTTCGTCTCGCTCTGTGCCCCCTTCTTCTTGTCTGTGTTCTTCCCTTCTTGCCTCT-3' (FRAG.  
NO:1229)
- (SEQ. ID NO:1239)
- 5'-GGGTGTGGTGTCCG-3' (FRAG. NO:1230) (SEQ. ID NO:1240)
- 5'-CTTGGCGTTCTTTCGGGTG-3' (FRAG. NO:1231) (SEQ. ID NO:1241)
- 5'-TTTCTTCTCTGGGTGGC-3' (FRAG. NO:1232) (SEQ. ID NO:1242)
- 5'-CTGCTGCTCGTGTGGT-3' (FRAG. NO:1233) (SEQ. ID NO:1243)

- 5'-GCTCCGCTCCCGGGTTC-3' (FRAG. NO:1234) (SEQ. ID NO:1244)  
 5'-GTCTCGCTCTGTGCCCC-3' (FRAG. NO:1235) (SEQ. ID NO:1245)  
 5'-CTTCCTTCCTTGTC-3' (FRAG. NO:1236) (SEQ. ID NO:1246)  
 5'-GTGTTCTCCCTTCCTTGCCTCT-3' (FRAG. NO:1237) (SEQ. ID NO:1247)  
 5'-GGGCBCGGGG CBGTGGGGG GCBGTGTGG GCBGGCBGCB GGGTGTGGT TCCBGGBBT BTGGGGBGGC BGBTGCBGG  
 5 GCGCBGGGG CBGTBGCBBT GBGGTBGCB GCGBGGCGTG CCGCGGBGBC CTTCBTGGTB CCTGTGGBGB GGCTGTCGG  
 GG-3' (FRAG. NO:1818) (SEQ. ID NO:1829)

### Human Muscarinic Acetylcholine Receptor HM1\* Anti-sense Oligonucleotide Fragments

- 5'-GCTGCCCGGC GGGGTGTGCG CTGGCGCTC CCGTGCTCGG TTCTCTGTCT CCCGTCCCC CTGCTGGC GTCTCGGGGC  
 10 TTCTCTCTCT TCCTCTTCTT CCTCCGCTC CGTGGGGGCT GCTTGGTGGG GGCCTGTGCTT CCGGGTCCCG GGGCTTCTGG  
 CCCTTGCCGT TCATGGTGGC TAGGTGGGG GTTCBTGGTG GCTBGGTGGG GC-3' (FRAG. NO:1819) (SEQ. ID NO: 1830)  
 5'-GGTGGGGC-3' (FRAG. NO:1820) (SEQ. ID NO: 1831)  
 5'-GCCCCGCGGGG-3' (FRAG. NO:1821) (SEQ. ID NO: 1832)  
 5'-CGG GGC TTC TGG CCC-3' (FRAG. NO:1822) (SEQ. ID NO: 1833)  
 5'-GTT CBT GGT GGC TBG GTG GGG C-3' (FRAG. NO:1238) (SEQ. ID NO:1248)  
 15 5'-GCT GCC CGG CGG GGT GTG CGC TTG GC-3' (FRAG. NO:1239) (SEQ. ID NO:1249)  
 5'-GCT CCC GTG CTC GGT TCT CTG TCT CCC GGT-3' (FRAG. NO:1240) (SEQ. ID NO:1250)  
 5'-CCC CCT TTG CCT GGC GTC TCG G-3' (FRAG. NO:1241) (SEQ. ID NO:1251)  
 5'-GCC TTC GTC CTC TTC CTT CTT CC-3' (FRAG. NO:1242) (SEQ. ID NO:1252)  
 20 5'-GCT CCG TGG GGG CTG CTT GGT GGG GGC CTG TGC CTC GGG GTC C-3' (FRAG. NO:1243) (SEQ. ID NO:1253)  
 5'-CGG GGC TTC TGG CCC TTG CC-3' (FRAG. NO:1244) (SEQ. ID NO:1254)  
 5'-GTT CAT GGT GGC TAG GTG GGG C-3' (FRAG. NO: 1245) (SEQ. ID NO:1255)

### Human Muscarinic Acetylcholine Receptor HM3\* Anti-sense Oligonucleotide Fragments

- 5'-GGG GTG GGT BGG CCG TGT CTG GGGTT GGC CBT GTT GGT TGC CTCT TGG TGG TGC GCC GGG CGCG TCT TGG CTT  
 25 TCT TCT CCT TCG GGC CCT CGG GCC GGT GCT TGT GGGCT CCT CCC GGG CGG CCT CCC CGG GCG GGG GCT TCT  
 TGGCG CTG GCG GGG GGG CCT CCGTCT CTG TGG CTG GGC GTT CCT TGG TGT TCT GGG TGGTGG CGG GCG TGG TGG  
 CCT CTG TGGGGG CCC GCG GCT GCB GGG GTTG CCT GTC TGC TTC GTCCTT TGC GCT CCC GGG CCG CCGGG GTG GGT  
 AGG CCG TGT CTG GGGTT GGC CAT GTT GGT TGC CCGG CCC GCG GCT GCA GGG G-3' (FRAG. NO:1823) (SEQ. ID  
 NO:1934)  
 30 5'-CCC GGG CGG-3' (FRAG. NO:1824) (SEQ. ID NO:1835)  
 5'-G GCG GGG GGG CC-3' (FRAG. NO:1825) (SEQ. ID NO:1836)  
 5'-CCC GGG CCG CC-3' (FRAG. NO: 1826) (SEQ. ID NO: 1837)  
 5'-GG CCG TGT-3' (FRAG. NO:1827) (SEQ. ID NO:1838)  
 5'-GGG GTG GGT BGG CCG TGT CTG GGG-3' (FRAG. NO:1246) (SEQ. ID NO:1256)  
 35 5'-GTT GGC CBT GTT GGT TGC C-3' (FRAG. NO:1247) (SEQ. ID NO:1257)  
 5'-TCT TGG TGG TGC GCC GGG C-3' (FRAG. NO:1248) (SEQ. ID NO:1258)  
 5'-GCG TCT TGG CTT TCT TCT CCT TCG GGC CCT CGG GCC GGT GCT TGT TGT GG-3' (FRAG. NO:1249) (SEQ. ID NO:1259)  
 5'-GCT CCT CCC GGG CGG CCT CCC CGG GCG GGG GCT TCT TG-3' (FRAG. NO:1250) (SEQ. ID NO:1260)  
 5'-GCG CTG GCG GGG GGG CCT CCT CC-3' (FRAG. NO:1251) (SEQ. ID NO:1261)  
 40 5'-GCT CTG TGG CTG GGC GTT CCT TGG TGT TCT GGG TGG C-3' (FRAG. NO:1252) (SEQ. ID NO:1262)  
 5'-TGG CCG GCG TGG TGG CCT CTG TGG TGG-3' (FRAG. NO:1253) (SEQ. ID NO:1263)  
 5'-GGG CCC GCG GCT GCB GGG G-3' (FRAG. NO:1254) (SEQ. ID NO:1264)  
 5'-TTG CCT GTC TGC TTC GTC-3' (FRAG. NO:1255) (SEQ. ID NO:1265)  
 5'-CTT TGC GCT CCC GGG CCG CC-3' (FRAG. NO:1256) (SEQ. ID NO:1266)  
 45 5'-GGG GTG GGT AGG CCG TGT CTG GGG-3' (FRAG. NO:1257) (SEQ. ID NO:1267)  
 5'-GTT GGC CAT GTT GGT TGC C-3' (FRAG. NO:1258) (SEQ. ID NO:1268)  
 5'-GGG CCC GCG GCT GCA GGG G-3' (FRAG. NO:1259) (SEQ. ID NO:1269)

### Human Fibronectin\* Antisense Oligonucleotide Fragments

- 5'-CGG TTT CCT TTG CGG TC TTG GCC CGG GCT CCG GGT G CCC GCC CGC CCG CCG GCC GCC GC CCC GCC GGG CTG  
 50 TCC CCG CCC CGC CCC GGC CCG GGG CGC GGG GG CGG CCC TCC CGC CCC TCT GG GCC GGC GCG GGC GTC GG CCG  
 CTC GCG CCT GGG GTT CCC TCT CCT CCC CCT GTG C GCC TGC CTC TTG CTC TTCTGC GTC CGC TGC CTT CTC CC CTC  
 TCC TCG GCC GTT GCC TGT GC TGT CCG TCC TGT CGC CCT TCC GTG GTG C TGT TGT CTC TTC TGC CCT C GGT GTG  
 CTG GTG CTG GTG GTG CCT CTG CCC GTG CTC GCCTG CCT GGG CTG GCC TCT TCG GGT GTG TCG GGG CTC  
 TCT TGG TTG CCC TTT CTT CTC GTG GTG CCT CTC CTC CCT GGC TTG GTC GT TGT CTG GGG TGG TGC TCC TCT CCC  
 55 TTT CCC TGC TGG CCG TTT GT  
 CCT GTT TTC TGT CTT CCT CT TTC CTC CTG TTT CTC CGT TTG GCT TGC TGC TTG CGG GGC TGT CTC C CTT GCC CCT  
 GTG GGC TTT CCC TGG TCC GGT CTT CTC CTT GGG GGT C GCC CTT CTT GGT GGG CTGGCT CGT CTG TCT TTT TCC TTC

- C TGG GGG TGG CCG TTG TGG GCG GTG TGG TCC GCC T TGC CTC TGC TGG TCT TTC-3' (FRAG. NO:1828) (SEQ. ID NO: 1839)
- 5'-GGCCCGGGC-3' (FRAG. NO:1829) (SEQ. ID NO: 1840)
- 5'-GCCGCGCGGGCG-3' (FRAG. NO:1830) (SEQ. ID NO:1841)
- 5'-GCCTGGGCTGGCC-3' (FRAG. NO:1831) (SEQ. ID NO: 1842)
- 5'-GGGGG TGGCCG-3' (FRAG. NO:1832) (SEQ. ID NO: 1843)
- 5'-GG GGG TGG CCG TTG TGG GCG G-3' (FRAG. NO:1833) (SEQ. ID NO: 1844)
- 5'-CGG TTF CCT TTG CGG TC-3' (FRAG. NO:1260)(SEQ. ID NO:1270)
- 5'-TTG GCC CGG GCT CCG GGT G-3' (FRAG. NO:1261)(SEQ. ID NO:1271)
- 5'-CCC GCC CGC CCG CCG GCC GCC GC-3' (FRAG. NO:1262)(SEQ. ID NO:1272)
- 5'-CCC GCC GGG CTG TCC CCG CCC CGC CCC-3' (FRAG. NO:1263)(SEQ. ID NO:1273)
- 5'-GGC CCG GGG CGC GGG GG-3' (FRAG. NO:1264)(SEQ. ID NO:1274)
- 5'-CGG CCC TCC CGC CCC TCT GG-3' (FRAG. NO:1265)(SEQ. ID NO:1275)
- 5'-GCC GGC GCG GGC GTC GG-3' (FRAG. NO:1266)(SEQ. ID NO:1276)
- 5'-CCG CTC GCG CCT GGG GTT CCC TCT CCT CCC CCT GTG C-3' (FRAG. NO:1267)(SEQ. ID NO:1277)
- 5'-GCC TGC CTC TTG CTC TTC-3' (FRAG. NO:1268)(SEQ. ID NO:1278)
- 5'-TGC CTC CGC TGC CTT CTC CC-3' (FRAG. NO:1269)(SEQ. ID NO:1279)
- 5'-CTC TCC TCG GCC GTT GCC TGT GC-3' (FRAG. NO:1270)(SEQ. ID NO:1280)
- 5'-TGT CCG TCC TGT CGC CCT TCC GTG GTG C-3' (FRAG. NO:1271)(SEQ. ID NO:1281)
- 5'-TGT TGT CTC TTC TGC CCT C-3' (FRAG. NO:1272)(SEQ. ID NO:1282)
- 5'-GGT GTG CTG GTG CTG GTG GTG GTG-3' (FRAG. NO:1273)(SEQ. ID NO:1283)
- 5'-CCT CTG CCC GTG CTC GCC-3' (FRAG. NO:1274)(SEQ. ID NO:1284)
- 5'-CTG CCT GGG CTG GCC TCT TCG GGT-3' (FRAG. NO:1275)(SEQ. ID NO:1285)
- 5'-GTG GCT TTG GGG CTC TCT TGG TTG CCC TTT-3' (FRAG. NO:1276)(SEQ. ID NO:1286)
- 5'-CTT CTC GTG CTG CCT CTC CTC CCT GGC TTG GTC GT-3' (FRAG. NO:1277)(SEQ. ID NO:1287)
- 5'-TGT CTG GGG TGG TGC TCC TCT CCC-3' (FRAG. NO:1278)(SEQ. ID NO:1288)
- 5'-TTT CCC TGC TGG CCG TTT GT-3' (FRAG. NO:1279)(SEQ. ID NO:1289)
- 5'-CCT GTT TTC TGT CTT CCT CT-3' (FRAG. NO:1280)(SEQ. ID NO:1290)
- 5'-TTC CTC CTG TTT CTC CGT-3' (FRAG. NO:1281)(SEQ. ID NO:1291)
- 5'-TTG GCT TGC TGC TTG CCG GGC TGT CTC C-3' (FRAG. NO:1282)(SEQ. ID NO:1292)
- 5'-CTT GCC CCT GTG GGC TTT CCC-3' (FRAG. NO:1283)(SEQ. ID NO:1293)
- 5'-TGG TCC GGT CTT CTC CTT GGG GGT C-3' (FRAG. NO:1284)(SEQ. ID NO:1294)
- 5'-GCC CTT CTT GGT GGG CTG-3' (FRAG. NO:1285)(SEQ. ID NO:1295)
- 5'-GCT CGT CTG TCT TTT TCC TTC C-3' (FRAG. NO:1286)(SEQ. ID NO:1296)
- 5'-TGG GGG TGG CCG TTG TGG GCG GTG TGG TCC GCC T-3' (FRAG. NO:1287)(SEQ. ID NO:1297)
- 5'-TGC CTC TGC TGG TCT TTC-3' (FRAG. NO:1288)(SEQ. ID NO:1298)

#### Human Interleukin-8\* Fragments Antisense Oligonucleotide Fragments

- 5'-GBTGTTTGT BCCBBBGCBT CBBGBBTGCG TTTGCTBTCT BBGGBTBCB TTTBGCBTB GGBBBBCGCT GTBGGTCBGBB
- BGBTGTGCTT BCCTTCBCBC BGBGCTGCBG BBTBCBGBBGG CTGCCBBGBGBG CCBGCGCCBGC TTGGBGTCTB
- GTTTBCBCB BGTGBGGTGC TCCGGTGGCT TTTTGCTTGT GTGCTCTGCT GTCTCTG TTC CTCCGGTGG TTTCTTCTG
- GCTCTTGTCC TTTCTTCTGG CCCTTGGCCC-3' (FRAG. NO:1834) (SEQ. ID NO:1845)
- 5'-G CTC CGG-3' (FRAG. NO:1835) (SEQ. ID NO:1846)
- 5'-CBBGBBTGCG-3' (FRAG. NO:1836) (SEQ. ID NO:1847)
- 5'-CBCBC BGTGBGGTGC-3' (FRAG. NO:1837) (SEQ. ID NO:1848)
- 5'-BCCBBBGCBT CBBGBBTGCG-3' (FRAG. NO:1838) (SEQ. ID NO:1849)
- 5'-GCCBBGBGBG CCBGCGCCBGC-3' (FRAG. NO:1839) (SEQ. ID NO:1850)
- 5'-GTG CTC CGG TGG CTT TTT-3' (FRAG. NO:1289)(SEQ. ID NO:1299)
- 5'-GCT TGT GTG CTC TGC TGT CTC TG-3' (FRAG. NO:1290)(SEQ. ID NO:1300)
- 5'-TTC CTT CCG GTG GTT TCT TCC TGG CTC TTG TCC T-3' (FRAG. NO:1291)(SEQ. ID NO:1301)
- 5'-TTC TCT TGG CCC TTG GCC C-3' (FRAG. NO:1292)(SEQ. ID NO:1302)
- 5'-GBTGTTTGT BCCBBBGCBT CBBGBBTGCG TTTGCTBTCT BBGGBTBCB TTTBGCBTB GGBBBBCGCT GTBGGTCBGBB
- BGBTGTGCTT BCCTTCBCBC BGBGCTGCBG BBTBCBGBBGG CTGCCBBGBGBG CCBGCGCCBGC TTGGBGTCTB
- GTTTBCBCB BGTGBGGTGC TCCGGTGGCT TTTTGCTTGT-3' (FRAG. NO:1840) (SEQ. ID NO:1851)

#### Human IL-8 Receptor Alpha Antisense Oligonucleotide Fragments

- 5'-ACAGGGGCTG TAATCTTCATC TGCAGGTGGC ATGCCAGTGA AATTAGATC ATCAAAATCC CACATCTGTG
- GATCTGTAAT ATTTGACATG TCCTCTTCAAG TTTCAGCAAT GGTGTGATCT AACTGAAGCA CCGGCCAGGB CBGGGGCTGT
- BBTCTTCTGC TGCBBGTGGC BTGCCBGTGB BBTBTBGTCT BTCCBBBTCC CBCBTCTGTG GTCTGTBBT BTTTGBCBTG
- TCCTCTTCTG TTTTCBGBB TGGTTTGTCT TBBCTGBBGC BCCGGCCBGG TGGCTCGGTG CTCTGCCCC TGTTGTTCG
- GCGCTCGGTG GTGTGGCCCC CTGTGGTGTCT TCGTTTCCCC CTCTTCTCT TTGTTCCGGG GTTCTTGTGG CCGGCTGCTT
- GTCTCGTTCC-3'

- (FRAG. NO:1841) (SEQ. ID NO:1852)  
 5'-CBGGGGC-3' (FRAG. NO:1842) (SEQ. ID NO:1853)  
 5'-GCBGGTGGC-3' (FRAG. NO:1843) (SEQ. ID NO:1854)  
 5'-GCGGCGCTC-3' (FRAG. NO:1844) (SEQ. ID NO:1855)  
 5'-TGGCTCGGTGCTTCTGCCCC (FRAG. NO:1293)(SEQ. ID NO:1303)  
 5'-TGTTGTTGCGGCGCTC (FRAG. NO:1294)(SEQ. ID NO:1304)  
 5'-GGTTGGTGTGGCCCTG (FRAG. NO:1295)(SEQ. ID NO:1305)  
 5'-TGGTGCTTCGTTTCC (FRAG. NO:1296)(SEQ. ID NO:1306)  
 5'-CCCTCTTCTCTTTGTC (FRAG. NO:1297)(SEQ. ID NO:1307)  
 5'-GGGGGTTCTTGTGGC (FRAG. NO:1298)(SEQ. ID NO:1308)  
 5'-GGGCTGCTGTCTCGTTCC (FRAG. NO:1299)(SEQ. ID NO:1309)  
 5'-ACAGGGGCTG TAATCTCATC TGCAGGTGGC ATGCCAGTGA AATTTAGATC ATCAAAATCC CACATCTGTG  
 GATCTGTAAT ATTTGACATG TCCTCTTTCAG TTTCAGCAAT GGTTGATCT AACTGAAGCA CCGGCCAGG-3' (FRAG. NO:1845)  
 (SEQ. ID NO:1856)  
 5'-B CBGGGGCTGT BBTCTTCBTC TGCBBGGTGGC BTGCCBTGB BBTBTBGTG BTBCCBBTCC CBCBTCTGTG GBTCTGTBBT  
 BTTTGBCBTG TCCTCTTCBG TTTCBGCBB TGGTTGTGTC TBBCTGBBGC BCCGGCCBGG-3' (FRAG. NO:1846) (SEQ. ID  
 NO:1857)

### Human GM-CSF Antisense Oligonucleotide Fragments

- 5'-CTTGBGCBGG BBGCTCTGGG GCBGGGBGCT GCBGGGGCCC BGGGGGGTGG CTTCCTGCBC TGTCBGBGT GCBCTGTGCC  
 BCBGCBGCBG CTGCBGGGCC BTCBGCTTCB TGGGGCTCTG GGTGGCBGGT CCBGCCBTGG GTCTGGGTGG GGCTGGGGCTG  
 CBGGCTCCCG GCGGTCCBGCCTGGGTCTG GGGGCTGGG CTGCBGGCTC CGGGCGGGCG GGTGCGGGCT GCGTGTGGG  
 GGCTGCCCCG CAGGCCCTGC GGTCCBGCBB TGGGTCTGGG GGCTGGGCTG CBGGCTCCCG GCGGGCGGGT GCGGGCTGCG  
 TGCTGGGGCG TGCCCGCAG GCCCTGC-3' (FRAG. NO:1847) (SEQ. ID NO: 1858)  
 5'-GBGCBGG BBG-3' (FRAG. NO:1848) (SEQ. ID NO: 1859)  
 5'-GCCBGBGCBGCBGC-3' (FRAG. NO:1849) (SEQ. ID NO: 1860)  
 5'-GGG TGC GGG C-3' (FRAG. NO:1850) (SEQ. ID NO: 1861)  
 5'-GGT CCB GCC BTG GGT CTG GG-3' (FRAG. NO:1300)(SEQ. ID NO:1310)  
 5'-GGC TGG GCT GCB GGC TCC GG-3' (FRAG. NO:1301)(SEQ. ID NO:1311)  
 5'-GCG GGC GGG TGC GGG CTG CGT GCT GGG-3' (FRAG. NO:1302)(SEQ. ID NO:1312)  
 5'-GGC TGC CCC GCA GGC CCT GC-3' (FRAG. NO:1303)(SEQ. ID NO:1313)  
 5'-CTTGBGCBGG BBGCTCTGGG GCBGGGBGCT GCBGGGGCCC BGGGGGGTGG CTTCCTGCBC TGTCBGBGT GCBCTGTGCC  
 BCBGCBGCBG CTGCBGGGCC BTCBGCTTCB TGGGGCTCTG GGTGGCBGGT CCBGCCBTGG GTCTGGGTGG GGCTGGGCTG  
 CBGGCTCCCG GC-3' (FRAG. NO:1851) (SEQ. ID NO: 1862)

### Human Tumor Necrosis Factor $\alpha$ Antisense Oligonucleotide Fragments

- 5'-GCBCCGCTG GBGCCCTGGG GCCCCCTGT CTCTTGGGG BGCCTCTCT CGGCCBGTG CBCGTCCCGG BTCBTGCTTT  
 CBGTGCTCBT GGTGTCTTT CCBGGGGGBB BGGGGGCTGG TCCTCTGCTG TCCTTGCTGG TGCTCBTGGT GTCCTTTCCG  
 CCTGGGGGCC CCCCTGTCTT CTGGGGCCT CTCCCTCTG GGGGCCGTCT CTCTCCCTCT CTGCGGTCTC TCTCTTCTC  
 TCTCTCTT CCCCTTCCC GCTCTTCTG TCTCGGTCTG TGGTTTCTC TCTCCGCTGG CTGCTGTCT GGCCTGCGCT  
 CTGGGCTGT GCTGTCTCT CTCCGGTTC TGTCCTCTCT GTCTGTCGCC CCTCTGGGG TCTCCCTCTG GGTGGTGGTC  
 TTGTTGCTTG GGCTGGGCTC CGTGTCTCCB GTGCTCBTGG TGTCGGCTGB GGGBGCCTCT GCTGGCGCTG GTCCTCTGTCTC  
 CTGCTGGTG CTCTGTGGT CTTTCCGCC CTGGGGCCCC CCGTCTCTCT TGGGGCCTCT TCCCTCTGGG GGCGGTCTC  
 TCTCCCTCTC TTGCGTCTCT CTCTTCTCT CTCTCTCTC CCTTTCGCC CTCTTCTGT CTCGGTGTCT GGTCTTCTCT  
 CTCGGCTGGC TGCTGTCTG GCCTGGGCTC TTGGCTGTG CTGTTCTCT TCCGGTCTCT GTCCTCTCTG TCTGTGCGCC  
 CCTCTGGGGT CTCCCTCTGG CGTGGTGGTC TTGTTGCTTG GGCTGGGCTC CGTGTCTCCB GTGCTCBTGG TGTCGGCTGB  
 GGGBGCCTCT GCTGGC-3' (FRAG. NO:1852) (SEQ. ID NO:1863)  
 5'-GGGGCCCCC-3' (FRAG. NO:1853) (SEQ. ID NO:1864)  
 5'-GGG GGC CG TCT-3' (FRAG. NO:1854) (SEQ. ID NO:1865)  
 5'-CCBGGGGGBB BGGGGGCTGG-3' (FRAG. NO:1855) (SEQ. ID NO:1866)  
 5'-GCBCCGCTGGBGCCCTGGGGCCCCCTGTCTTCTTGGGGBGGCCTCTCGCCBGTCCBCGTCCCGGTCBTGCTTTCTGCTG  
 TCBTGGTGTCTTTCCBGGGGGBBGGGG-3' (FRAG. NO:1304) (SEQ. ID NO:1314)  
 5'-GCT GGT CCT CTG CTG TCC TTG CTG GTG CTC BTG GTG TCC TTT CC GCC CTG GGG CCC CCC TGT CTT CTT GGG G  
 CCT CTT CCC TCT GGG GGC CG TCT CTC TCC CTC TCT TGC GTC TCT C TCT TTC TCT CTC TCT CTT CCC C TTT CCC GCT  
 CTT TCT GTC TC GGT GTC TGG TTT TCT CTC TCC GCT GGC TGC CTG TCT GGC CTG CGC TCT T GGC CTG TGC TGT TCC  
 TCC TCC GGT TCC TGT CCT CTC TGT CTG TC GCC CCC TCT GGG GTC TCC CTC TGG C GTG GTG-GTC TTG TTG CTT GGG  
 CTG GGC TCC GTG TCT C CBG TGC TCB TGG TGT CC-3' (FRAG. NO:1305) (SEQ. ID NO:1315)  
 5'-GCT GBG GGB GCG TCT GCT GGC GGT CCT CTG CTG TCC TTG CTG GTG CTC BTG GTG TCC TTT CC GCC CTG GGG  
 CCC CCC TGT CTT CTT GGG G CCT CTT CCC TCT GGG GGC CG TCT CTC TCC CTC TCT TGC GTC TCT C TCT TTC TCT CTC  
 TCT CTT CCC C TTT CCC GCT CTT TCT GTC TC GGT GTC TGG TTT TCT CTC TCC GCT GGC TGC CTG TCT GGC CTG CGC

- TCT T GGC CTG TGC TGT TCC TCC TCC GGT TCC TGT CCT CTC TGT CTG TC GCC CCC TCT GGG GTC TCC CTC TGG C  
GTG GTG GTC TTG TTG CTT GGG CTG GGC TCC GTG TCT C CBG TGC TCB TGG TGT CC GCT GBG GGB GCG TCT GCT GGC-  
3'
- (FRAG. NO:1306) (SEQ. ID NO:1316)
- 5 5'-GCT GGT CCT CTG CTG TCC TTG CTG-3' (FRAG. NO:1655) (SEQ. ID NO:1665)  
5'-GTG CTC BTG GTG TCC TTT CC-3' (FRAG. NO:1656) (SEQ. ID NO:1666)  
5'-GCC CTG GGG CCC CCC TGT CTT CTT GGG G-3' (FRAG. NO:1657) (SEQ. ID NO:1667)  
5'-CCT CTT CCC TCT GGG GGC CG-3' (FRAG. NO:1658) (SEQ. ID NO:1668)  
5'-TCT CTC TCC CTC TCT TGC GTC TCT C-3' (FRAG. NO:1659) (SEQ. ID NO:1669)  
10 5'-TCT TTC TCT CTC TCT CTT CCC C-3' (FRAG. NO:1660) (SEQ. ID NO:1670)  
5'-TTT CCC GCT CTT TCT GTC TC-3' (FRAG. NO:1661) (SEQ. ID NO:1671)  
5'-GGT GTC TGG TTT TCT CTC TCC-3' (FRAG. NO:1662) (SEQ. ID NO:1672)  
5'-GCT GGC TGC CTG TCT GGC CTG CGC TCT T-3' (FRAG. NO:1663) (SEQ. ID NO:1673)  
5'-GGC CTG TGC TGT TCC TCC-3' (FRAG. NO:1664) (SEQ. ID NO:1673)  
15 5'-TCC GGT TCC TGT CCT CTC TGT CTG TC-3' (FRAG. NO:1665) (SEQ. ID NO:1675)  
5'-GCC CCC TCT GGG GTC TCC CTC TGG C-3' (FRAG. NO:1666) (SEQ. ID NO:1676)  
5'-GTG GTG GTC TTG TTG CTT-3' (FRAG. NO:1667) (SEQ. ID NO:1677)  
5'-GGG CTG GGC TCC GTG TCT C-3' (FRAG. NO:1668) (SEQ. ID NO:1678)  
5'-CBG TGC TCB TGG TGT CC-3' (FRAG. NO:1669) (SEQ. ID NO:1679)  
20 5'-GCT GBG GGB GCG TCT GCT GGC-3' (FRAG. NO:1670) (SEQ. ID NO:1680)

#### Human Leukotriene C4 Synthase Antisense Oligonucleotide Fragments

- 5'-CTCGGTBGB C GCGCTCGBB C TCGGGTGGG C CGGTGGTGBG CGGCGGCBBCB CGCGBBGGC CCTGCGCGCC  
GBGBTCBCTG CBGGGBBBG TBGGCTTGC B GCBGBBCTCC CBGGBGGGTG BCBGCBGCCB GTBGBGCTBC CTCGTCCTTC  
BTGGTBCCGT CGGTGTGGTG GCBGCGGGCTG TGTGTGBBGG CBGCTGGGC CCCGTCTGCT GCTCCTGCTG CCGCCTCGTC  
25 CTCA TGG TA CCGTCGGTGT GGTGGCCTCG GGTGGGCGG TGGTGGGCG CGCGCGCTCG CGTGGCTCCG GCTCTTCTTT  
CCCCGCTCCG CGGCCCGGG GCCTTGTCT CCGCTGCTCT TCBTGGTBCC G-3' (FRAG. NO:1856) (SEQ ID NO: 1867)  
5'-GCB GCBGGBC-3' (FRAG. NO:1857) (SEQ ID NO: 1868)  
5'-CCCGGCTCCG-3' (FRAG. NO:1858) (SEQ ID NO: 1869)  
5'-CGGCCCCGGG GCC-3' (FRAG. NO:1859) (SEQ ID NO: 1870)  
30 5'-CB CGCGG-3' (FRAG. NO:1860) (SEQ ID NO: 1871)  
5'-GCC CCG TCT GCT GCT CCT CGT GCC G-3' (FRAG. NO:1307) (SEQ. ID NO:1317)  
5'-CCT CGT CCT TCA TGG TAC CGT CGG TGT GGT GGC-3' (FRAG. NO:1308) (SEQ. ID NO:1318)  
5'-CTC GGG TGG GCC GGT GGT G-3' (FRAG. NO:1309) (SEQ. ID NO:1319)  
5'-GGG CGC GCG CGC TCG CGT-3' (FRAG. NO:1310) (SEQ. ID NO:1320)  
35 5'-GCC TCC GGC TCT TCT CCG GCT CCG TCG GCC CGG GGT CCT TGG TCT C-3' (FRAG. NO:1311) (SEQ. ID NO:1321)  
5'-CCT CGT CCT TCB TGG TBC CG-3' (FRAG. NO:1312) (SEQ. ID NO:1322)  
5'-CTCGGTBGB C GCGCTCGBB C TCGGGTGGG C CGGTGGTGBG CGGCGGCBBCB CGCGBBGGC CCTGCGCGCC  
GBGBTCBCTG CBGGGBBBG TBGGCTTGC B GCBGBBCTCC CBGGBGGGTG BCBGCBGCCB GTBGBGCTBC CTCGTCCTTC  
BTGGTBCCGT CGGTGTGGTG GCBGCGGGCTG TGTGTGBBGG CBGCTGG-3' (FRAG. NO:1861) (SEQ ID NO: 1872)

#### Human Endothelin-1 Antisense Oligonucleotide Fragments

- 5'-BCCGGCGGBG CCGCCBGGT GGBCTGGGBG TGGGTTCTC CCCGCCGTC TBCCCBCCG CGCTGBGCTC BGCCTTBBG  
BCTGCTGTTT CTGGBGCTCC TTGGCBGGC GGBBGGCB GBGGBBBBT CBTGGBBBB TBBTCCBTTC TGBBBBBBBB  
GGBTCBBBBB CCTCCGTTT CCGTTGCCG TGGCGGCGC TGGGGTTCC TCGTGGGTTT CTCCCGCGC TTCTCCGGTC  
TGTTGCCCTT GTGGGCTTCT GTCTTTTTC GCTGTCTTT TCCTGCTTGG CGTCTTTTCC TTCTTTTGTG CTCGGTTGTG  
45 GGTCCGCTGG TCCTTTGCCG TGTGTGTTT TGCTGCCGT TCGCCTGGCG CGCGCTGCGG GTTCTCTGTG GGTTCCTCCC  
CGCGGTTCTC CGGTCTGTTG CTTTGTGGG CTTCTGTCT TTTTGGCTGT TCTTTCTG CTGGCGTCT TTTCTTTCT  
TTGTGCTCGG TTGTGGTCC GCTGGTCTT TGCCTGTGT GTTCTGCTG-3' (FRAG. NO:1862) (SEQ. ID NO:1873)  
5'-CCGGCGGBG CCGCCBGGT GGB-3' (FRAG. NO:1863) (SEQ. ID NO:1874)  
5'-CCGCCBGGG-3' (FRAG. NO:1864) (SEQ. ID NO:1875)  
50 5'-GGCGCGCGC-3' (FRAG. NO:1865) (SEQ. ID NO:1876)  
5'-GTGGGTCCGC-3' (FRAG. NO:1866) (SEQ. ID NO:1877)  
5'-CCCGTTCCGCTGGCGC-3' (FRAG. NO:1313) (SEQ. ID NO:1323)  
5'-GCGCTCGCGGTTCTCT-3' (FRAG. NO:1314) (SEQ. ID NO:1324)  
5'-GTGGGTTTCTCCCGCGGTTCTCT-3' (FRAG. NO:1315) (SEQ. ID NO:1325)  
55 5'-CGGTCTGTTGCCCTTTGTGGG-3' (FRAG. NO:1316) (SEQ. ID NO:1326)  
5'-CTTCTGTCTTTTGGCT-3' (FRAG. NO:1317) (SEQ. ID NO:1327)  
5'-GTCTTTTCTGCTTGGC-3' (FRAG. NO:1318) (SEQ. ID NO:1328)  
5'-GTCTTTTCTTCTTCT-3' (FRAG. NO:1319) (SEQ. ID NO:1329)  
5'-TGTGCTCGGTTGTGGGTC-3' (FRAG. NO:1320) (SEQ. ID NO:1330)  
60 5'-CGCTGCTCCTTGGC-3' (FRAG. NO:1321) (SEQ. ID NO:1331)

- 5'-CTGTGTGTTTCTGCTG-3' (FRAG. NO:1322)(SEQ. ID NO:1332)  
 5'-CCCCTTCGCCTGGCGC-3' (FRAG. NO:1323)(SEQ. ID NO:1333)  
 5'-GCCCTGCGGGTTCTC-3' (FRAG. NO:1324)(SEQ. ID NO:1334)  
 5'-GTGGGTTTCTCCCGCCGTTCTC-3' (FRAG. NO:1325)(SEQ. ID NO:1335)  
 5'-CGGTCTGTGCTTTGTGGG-3' (FRAG. NO:1326)(SEQ. ID NO:1336)  
 5'-CTTCTGTCTTTTGGCT-3' (FRAG. NO:1327)(SEQ. ID NO:1337)  
 5'-GTTCTTTTCTGCTTGGC-3' (FRAG. NO:1328)(SEQ. ID NO:1338)  
 5'-GTCTTTTCTTTCTT-3' (FRAG. NO:1329)(SEQ. ID NO:1339)  
 5'-TGCTGCTCGGTTGTGGTC-3' (FRAG. NO:1330)(SEQ. ID NO:1340)  
 5'-CGCTGGTCCTTTGCC-3' (FRAG. NO:1331)(SEQ. ID NO:1341)  
 5'-CTGTGTGTTTCTGCTG-3' (FRAG. NO:1332)(SEQ. ID NO:1342)

### Endothelin Receptor ET-B Antisense Oligonucleotide Fragments

- 5'-GCCCTGTGCG GCGGGAAGCC TCTCTCTCT CCCCAGATC CGCGACAGGC CGCAGGCAAG AACCAGCGCA ACCAGGGCGC  
 GTCCGCACAG ACTTGGAGGC GGCTGCATGC TGCTACCTGC TCCAGAAGCG TCCGGTGGCC GCCGCGCC CTGTGGGGCG  
 GGBBGCTCT CTCCTCTCCC CBGTCCGCG BCBGGCCGB GGCBBGBBCC BGCGBBCCB GGGCGCGTCC GCBCBGBCTT  
 GGBGGCGGCT GCBTGCTGCT BCCTGCTCGGGCG GGBBGCTCCG GTGGCCGCCG CGCGTCCGCT GGCCGCCGCG  
 CCTCTCTCT CTCCCGTGG CCCTGTCGGG CGGGTCTGC CGTCTGTCT CTTTCTTT TGCTGTCTTG TCTTCCCGTC  
 TCTGCTTT-3' (FRAG. NO: 1867) (SEQ. ID NO: 1878)  
 5'-CGGGCG GGBBGCC-3' (FRAG. NO: 1868) (SEQ. ID NO: 1879)  
 5'-CGGGCGGG-3' (FRAG. NO: 1869) (SEQ. ID NO: 1880)  
 5'-CCGCBGBBC-3' (FRAG. NO: 1870) (SEQ. ID NO: 1881)  
 5'-GCGTCCGGTGGCCGCCG-3' (FRAG. NO:1333)(SEQ. ID NO:1343)  
 5'-GCCTCTCTCTCTCCCC-3' (FRAG. NO:1334)(SEQ. ID NO:1344)  
 5'-GTGGCCCTGTGCGGGCGG-3' (FRAG. NO:1335)(SEQ. ID NO:1345)  
 5'-TCCTGCGCTCTGTCTCTTT-3' (FRAG. NO:1336)(SEQ. ID NO:1346)  
 5'-TCTTTTGTCTTGT-3' (FRAG. NO:1337)(SEQ. ID NO:1347)  
 5'-CTTCCGCTCTGTCTT-3' (FRAG. NO:1338)(SEQ. ID NO:1348)  
 5'-GCCCTGTGCG GCGGGAAGCC TCTCTCTCT CCCCAGATC CGCGACAGGC CGCAGGCAAG AACCAGCGCA ACCAGGGCGC  
 GTCCGCACAG ACTTGGAGGC GGCTGCATGC TGCTACCTGC TCCAGAAGCG TCCGGTGGCC GCCGC-3' (FRAG. NO: 1871)  
 (SEQ. ID NO: 1882)  
 5'-GCCCTGTGCG GCGGGBBGC TCTCTCTCT CCCCGBTCC GCGBCBGGCC GCBGGCBGB BCCBGCGB BCCBGGGCGC  
 GTCCGCBGB BCTTGBBGC GGCTGCTGC TGCTBCCTGC TCCBGBBGC TCCGGTGGCC GCCGC-3' (FRAG. NO: 1872)  
 (SEQ. ID NO: 1883)

### Endothelin ETA Receptor Antisense Oligonucleotide Fragments

- 5'-GTCTGTCTC CCCGTCTCT CCACTGCTT CTCCCGGGG CTTCGCCGC TTCGGGTGGC CGGTGTCCCG GGCTCCGGCG  
 CGCGCGCGC TTCGGTGGC GGTGGGTGGC GCGGGCTGCC GGGTCCGCG GCGCGCTGGC CCCTGTGCT GCTTTTGTCT  
 TGTTCCGTTT TGCTGTCTC GGTCTGTGT GTGGTTGTTT TGTTCTTCT TGGGTGTGGG CTTGCGGTT TTGGCTGTGG  
 GCCCTTTGGG GCCTTGGCTT CTGGCTGCT TGCTCTCCC GTCTCTCCC ACTGCTTCT CCCGGGGGCT TCCCGGGCTT  
 CGGGTGGCG GTGTCCCGG CTCCGGCGG GCGGGGCTT CGGTGCGGG TGGGTGGCG GGGCTGCCG GTCCGCGCG  
 CGCCTGGGC CTGTGCTGC TTTTGCTTG TTCCGTCTG GCTGCTCCG TCTGTGTTG GGTGTTTG TTTCTTCTT  
 GGTGTGGGC TTGCGGTTT GGCTGTGGC CTTTGGGGC CTGGCTTCT GGCTCCAT CCACATGATT GCTTAGATT  
 GTGCTGATC TCTCAGGATT ATCACTGATT ACACATCAA CCAGTGCCAG CCAAAAGGAT GCCCTGAGGC AAAGGGTTT  
 CATCTTGAAG CAAATTGAG GACBTCCB BTGTTGCTT BGTGTTGTC TGTBTCTCT BGGTTBTCT CTGTTTBCB  
 BTCCBCCBG TGCCBCCBB BBGGTGCC TGBGGCBBB GGTTCBCT TTGBGGCBB TTTBGGGB-3' (FRAG. NO:1873)  
 (SEQ. ID NO: 1884)  
 5'-GBGGCBGGG-3' (FRAG. NO:1874) (SEQ. ID NO: 1885)  
 5'-GCCBGCBB BBGG-3' (FRAG. NO:1875) (SEQ. ID NO: 1886)  
 5'-CGCTGGGCC C-3' (FRAG. NO:1876) (SEQ. ID NO: 1887)  
 5'-GTCTGTCTCCCGTCTCTCCC-3' (FRAG. NO:1339)(SEQ. ID NO:1349)  
 5'-ACTGCTTCTCCCGGG-3' (FRAG. NO:1340)(SEQ. ID NO:1350)  
 5'-GCTTCCCGGCTTC-3' (FRAG. NO:1341)(SEQ. ID NO:1351)  
 5'-GGGTGGCGGTGTCCCGGGCTCCGCGCGCGGC-3' (FRAG. NO:1342)(SEQ. ID NO:1352)  
 5'-GGCTTCGGCTGC-3' (FRAG. NO:1343)(SEQ. ID NO:1353)  
 5'-GGGTGGGTGCGCGG-3' (FRAG. NO:1344)(SEQ. ID NO:1354)  
 5'-GCTGCGGGTCCGCGCGGCGCTGGGCC-3' (FRAG. NO:1345)(SEQ. ID NO:1355)  
 5'-CTGTGCTGCTTTT-3' (FRAG. NO:1346)(SEQ. ID NO:1356)  
 5'-TGCTGTGCTGCTT-3' (FRAG. NO:1347)(SEQ. ID NO:1357)  
 5'-TGGCTGCTCCGCTGTGTTGTGGTTGTTT-3' (FRAG. NO:1348)(SEQ. ID NO:1358)



- 5'-TTTCTTCTTGGGTGTGGG-3' (FRAG. NO:1349)(SEQ. ID NO:1359)  
 5'-CCTTGC GGTTTGG-3' (FRAG. NO:1350)(SEQ. ID NO:1360)  
 5'-CTGTGGGCCCTTTG-3' (FRAG. NO:1351)(SEQ. ID NO:1361)  
 5'-GGGCCTTGGCTTCTGGTC-3' (FRAG. NO:1352)(SEQ. ID NO:1362)  
 5'-CATCCACATG ATTGCTTAGA TTTGTGCTGT ATCTCTCAGG ATTATCACTG ATTACACATC CAACCAAGTGC CAGCCAAAAG  
 GATGCCCTGA GGCAAAGGGT TTCCATCTTG AGGCAAATTT GAGGA-3' (FRAG. NO:1353)(SEQ. ID NO:1363)  
 5'-CBTCCBCBTG BTTGCTTBGB TTTGTGCTGT BTCTCTCBGG BTBTCTCBCTG BTTBCBCBTC CBCCCBGTGC CBGCCBBBGG  
 GBTGCCCTGB GGCBBBGGGT TTCCBTCTTG BGGCBBT TT GBGG-3' (FRAG. NO:1354)(SEQ. ID NO:1364)

### Substance P Antisense Oligonucleotide Antisense Oligonucleotide Fragments

- 10 5'-CTGCTBGGC TTGGGTCTCC GGGCGBTTCT CTGCBGBBGG TGCTCBBBGG GCTCCGGGCG TTCCTCCTTG BTCTGGTCGCT  
 GTCGTCCBG TCGGBCCBG BTTTCBGTCT BTCTTTGGCT CCTBTCTT CTGCBGBBGG CTGCGTGGG BCBGBBBBB  
 BGBCTGCCB GGCCBCBGG BTTTCTBTGT TGGTTTTG GBCGBCBGT CCCGCGGGGT GCTGAGTTT TCTGGTTCCT  
 CCGBGGCGB GTGGTCGCTC CGCGTTCTC TGGTCTCTCC GGTCCCGCG GGTGCTGTCT GGTGCTGTG GTGGCTTGG  
 TCTCGGGCG GTTCTCTCC TTTCCGC-3' (FRAG. NO:1877) (SEQ ID NO: 1888)  
 15 5'-CTCC GGGCB-3' (FRAG. NO:1878) (SEQ ID NO: 1889)  
 5'-GGCCBCBGG-3' (FRAG. NO:1879) (SEQ ID NO: 1890)  
 5'-GGGTCTCCGGGCG-3' (FRAG. NO:1880) (SEQ ID NO: 1891)  
 5'-GGG TCTCCGGGCG G-3' (FRAG. NO:1881) (SEQ ID NO:1892)  
 5'-CGTGGTCGCTCCGC-3' (FRAG. NO:1355)(SEQ. ID NO:1365)  
 20 5'-GTTTCTCTGGTTCCTCCG-3' (FRAG. NO:1356)(SEQ. ID NO:1366)  
 5'-GTCCCGCGGGGTCTG-3' (FRAG. NO:1357)(SEQ. ID NO:1367)  
 5'-TCTGTGCTGCTGCTG-3' (FRAG. NO:1358)(SEQ. ID NO:1368)  
 5'-GGCTTGGTCTCCGGGCG-3' (FRAG. NO:1359)(SEQ. ID NO:1369)  
 5'-GTTTCTCTCTTTCCGC-3' (FRAG. NO:1360)(SEQ. ID NO:1370)  
 25 5'-CTGCTBGGC TTGGGTCTCC GGGCGBTTCT CTGCBGBBGG TGCTCBBBGG GCTCCGGCBG TTCCTCCTTG BTCTGGTCGCT  
 GTCGTCCBG TCGGBCCBG BTTTCBGTCT BTCTTTGGCT CCTBTCTT CTGCBBCBG CTGCGTGGG BCBGBBBBB  
 BGBCTGCCB GGCCBCBGG BTTTCTBTGT TGGTTTTG GBCGBCBGT CCCGCGGGGT GCTGAGTTT TCTGGTTCCT  
 CCGBGGCGB-3' (FRAG. NO:1882) (SEQ ID NO: 1893)

### Substance P Receptor Antisense Oligonucleotide Fragments

- 30 5'-GGGCTBBGBT GBTCCBCBTC BCTBCCBCGT TGCCCBCCBC BGBGGTCBCC BCBTGBCCG TGTBGGCBGC TGCCBBBGG  
 BCBTTTGCC BGGCTGGTTG CCBGBBCTGB TTGGGTTGG BGGTGTBTGT GGBGTGTTT GGGGBBGGT CTGBGTCCBC  
 CGGBGGBCG TBTCCBTTT CGBBGTBGG CGGBBGGC CTBCTBTCTG TBCBCBCC CCCTCTGCBG CBGBGTCTG  
 TCGTGGCGCC TGGGGCTCBG GGTCCGGG TAAGATGATC CACATCACTA CCACGTTGCC CACCACAGAG GTCAACACAA  
 TGACCGTGA GGCAGTCCC CAAAGGACAA TTGCCAGGC TGGTGCACG AACTGATTGG GTTCCGAGGT GTTAGTGGAG  
 35 ATGTTTGGG AGAGGTCTGA GTCCACCGG AGGACGTTAT CCATTTGAA GCTAGGCGGT AAAGCCCTAC TATCTGTACA  
 CAACCCCT CTGCAGAGA GTCTGTCTG GCGCCTGGG GCTCAGGTC CGTCTGTG TGGCGCTGG GGCTCTTCTT  
 TTGTGGGCT TTTGGTGGCT GTGGCTGTG TCTGTGTTG TGTGCTGGG TGTGGCTTG GGGCCGTCT  
 CTGGCTCTC CTCGTGGGCC CCC-3' (FRAG. NO:1883) (SEQ. ID NO:1894)  
 5'-GGGBGGBCG-3' (FRAG. NO:1884) (SEQ. ID NO:1895)  
 40 5'-GGGTC CG-3' (FRAG. NO:1885) (SEQ. ID NO:1896)  
 5'-GGGCC CCC-3' (FRAG. NO:1886) (SEQ. ID NO:1897)  
 5'-GTCTGTCTGTCGCTGGGCTGGGCTC-3' (FRAG. NO:1361)(SEQ. ID NO:1371)  
 5'-TTCTTTTGTGGCT-3' (FRAG. NO:1362)(SEQ. ID NO:1372)  
 5'-CTTTGGTGGCTGTGGCTG-3' (FRAG. NO:1363)(SEQ. ID NO:1373)  
 45 5'-TGGTCTCTGTGGTTG-3' (FRAG. NO:1364)(SEQ. ID NO:1374)  
 5'-CTGCCCTGGGTCTGG-3' (FRAG. NO:1365)(SEQ. ID NO:1375)  
 5'-GGGTGTGGCTTGGGGCGTCTCTGGCTCTCTGTTGGGCCCC (FRAG. NO:1366)(SEQ. ID NO:1376)  
 5'-GGGCTAAGATGATCCACATC ACTACCAGT TGCCACCAC AGAGGTACCA ACAATGACCG TGAGGCAGC TGCCCAAAGG  
 ACAATTGCC AGGTGGTTG CACGAAGTGA TTGGTTCCG AGGTGTTAGT GGAGATGTTT GGGGAGAGGT CTGAGTCCAC  
 50 CGGGAGGACG TTATCCATTTC GAAGCTAGG GGTAAAGCCC TACTATCTGTA CACAACCCCT CTCTGCAGCA GAGTCTGT  
 GTGGCGCTG GGGCTCAGGTCC-3' (FRAG. NO:1367)(SEQ. ID NO:1377)  
 5'-GGGCTBBGBT GBTCCBCBTC BCTBCCBCGT TGCCCBCCBC BGBGGTCBCC BCBTGBCCG TGTBGGCBGC TGCCBBBGG  
 BCBTTTGCC BGGCTGGTTG CCBGBBCTGB TTGGTTCCG BGGTGTBTGT GGBGTGTTT GGGGBBGGTC TGBGTCCBC  
 GGBGBBCT BTCTCTTTC GGBGCTBGGC GGTBBGCCC BTCTBTCTGTB CCBBCCCCT CTCTGCBGB GBGTCTGT  
 55 GTGGCGCTG GGGCTCBGGG TCC-3' (FRAG. NO:1368) (SEQ. ID NO:1378)

### Chymase Antisense Oligonucleotides Antisense Oligonucleotide Fragments

5'-GGBGCTGBTB CTGCBGATTT CBGBGGBBG BBCCCTGBTB CTCBCCBGCT TCBGCTCTGG BGCBCBBGB BBBGBGCBG  
 BGGGGGBGB GBBGBBGBG CBTCTCCCB GBGBGGCTGC CTBGCBBBT GCTGGTTTTC CTTTCCBGTCT TTGGTTTTTB

- TBBCTCCCBG BBGGCBGBG BGGGGCBGG CGTTTTCTTC TCTCGCTGGT TTTCCTTTCC TGGCAGTGGG TGGGGGTGGG  
GGTGGGGTGG CTTCCTTGT CTGCGGGGTG TCCTTGTCT CTGGGCTTTT CTCCCTTTT CTTCTCTGT TGTTCCTGT  
GGGCTCTCT CTGTCTGT GTCTTGCC TGGCCCTCTT CCCTCTCTG TCTCTGTCC CTGTGTCCG CCCGTCTCC  
CTCTCTGAC CTCTTTTCC TCCGCTGGG GGGGCCCTGC CTGTCTCTG CTCCCTGGCT TGGGGTTTCT TCTGTGTGT  
5 TTCTCTCT GTTGGCTGGC TTCTCTCTT TTTGTCTT CTGGGTGCC CTCTCTCTT TCTTGGGTCC TTGGTCTGT  
GGCTGGG-3' (FRAG. NO:1887) (SEQ. ID NO:1898)  
5'-GGBGCBGBG-3' (FRAG. NO:1888) (SEQ. ID NO:1899)  
5'-GGBGCBGC-3' (FRAG. NO:1889) (SEQ. ID NO:1900)  
5'-GGGCBGBG CG-3' (FRAG. NO:1890) (SEQ. ID NO:1901)  
10 5'-CGTTTTCTTCTCTC-3' (FRAG. NO:1369)(SEQ. ID NO:1379)  
5'-GCTGGTTTCTCTTCC-3' (FRAG. NO:1370)(SEQ. ID NO:1380)  
5'-TGGCAGTGGGTGGGGGTGGGGGTGGG-3' (FRAG. NO:1371)(SEQ. ID NO:1381)  
5'-TTCTTGTCTCTGGGGGTGTCT-3' (FRAG. NO:1372)(SEQ. ID NO:1382)  
5'-CTTGCTCTGGGCTTTTCT-3' (FRAG. NO:1373)(SEQ. ID NO:1383)  
15 5'-CCCTTTTCTCTCC-3' (FRAG. NO:1374)(SEQ. ID NO:1384)  
5'-TGCTGTCTTCTCTGGG-3' (FRAG. NO:1375)(SEQ. ID NO:1385)  
5'-CTCTCTCTGTCTCTGT-3' (FRAG. NO:1376)(SEQ. ID NO:1386)  
5'-CCTTGCCCTGGCC-3' (FRAG. NO:1377)(SEQ. ID NO:1387)  
5'-TCTTCCCTCTCTCTCTGT-3' (FRAG. NO:1378)(SEQ. ID NO:1388)  
20 5'-CCCTGTCTCTCGCC-3' (FRAG. NO:1379)(SEQ. ID NO:1389)  
5'-GTCTTCTCTCTCTG-3' (FRAG. NO:1380)(SEQ. ID NO:1390)  
5'-ACCTCTTTCTCTCCG-3' (FRAG. NO:1381)(SEQ. ID NO:1391)  
5'-CTGGGTGGGGCCCTG-3' (FRAG. NO:1382)(SEQ. ID NO:1392)  
5'-CTGTCTCTCTCTCTCC-3' (FRAG. NO:1383)(SEQ. ID NO:1393)  
25 5'-TGGCTTGGGGTTCTCTG-3' (FRAG. NO:1384)(SEQ. ID NO:1394)  
5'-TGCTCTCTCTCTCTGT-3' (FRAG. NO:1385)(SEQ. ID NO:1395)  
5'-GGCTGGCTTCTCTCT-3' (FRAG. NO:1386)(SEQ. ID NO:1396)  
5'-TTTGTCTCTCTGGG-3' (FRAG. NO:1387)(SEQ. ID NO:1397)  
5'-TGCCCTTCTCTCTTCTGGG-3' (FRAG. NO:1388)(SEQ. ID NO:1398)  
30 5'-TCTTGTGTCTGGGCTGGG-3' (FRAG. NO:1389)(SEQ. ID NO:1399)  
5'-GGBGCTGTB CTGCBGATTT CBGBGGBBG BBCCCTGTB CTBCCBGCT TCBGCTCTGG BGCBCBBBG BBBGBGCBGC  
BGGGGGBBG CBGBBGBG CBCTCTCCB GBGBGGCTG CTGBGCBBT GCTGGTTTC CTTCBGTG TTGGGTTTTB  
TBBCTCCCBG BBGGCBGBG BGGGGCBGG-3' (FRAG. NO:1891) (SEQ. ID NO:1902)

### Endothelial Nitric Oxide Synthase Antisense Oligonucleotide Fragments

- 35 5'-GCGTCTTGGG GTGCBGGGCC CBCTCTGTG CGCTGGGCG CTGCTGTGCG TCCGTCTGCT GGGGGGCGG GGTGGCTGGG  
CCCTGCTTG CGACGACCC CGGGCCGACC CGAGGCTCG GGGCTGTGT TCTGGCGTG GTGGGCTTG GCCCTCTGG  
GGGCTGGGT TCCTGTGCG CTTGGGCGCT GGCCTCTTG GGTGCGGGG CGGGGGCGG GGGGGCGCT GTTCTGGGC  
CTGGGGGTG CTGTGGTGC CGTTGCCCG GGTGGTGGC GCGCTCTGC TGCCGGTCT TGGCTGGGT CCCCCGCGG  
40 TTCTCTGGG TCGCGTGGG GTGCTCGGT TCCTGTGCG GCTGTGCTT TGTCTTCCG GCGGTGGCG CGTGGTGGT  
CGCCCCCTT GGCCTTCTG TCGGGTCTG GCTGGTGGC GGTGCCCTT GCGGCGGTCT TCTCTCTGT GGTCTGGGC  
CCGGCGGTG TCGGGCTCT CGTGTCTGT CTGTGCTGT TCCGGCGCT CTTCTCTT CCGCCGCGC CGCTCCCGC  
CCGCTCTGC CCCTGGCCG GCTCTCTCT GCGGCTGT TCGGGGCGG GCCTTGGCG TCCGTTGGG GCTGCTCTG  
GCGTTCCG CCCTGGCCT GGGCGCTCT TCCGCTGT GCTGGTGGC CTCGTGGGC CCTCTGGC TCCGTTGCC  
45 TGTGTCCC CGGCTGTG CCGGGCGGT TGGGCGGGG TGGGCGCGG CGGCTCTCC GGGTGCCT TCTCCGCGG  
GGGTCCGCG CTCTGTGT TCCCTGGGT CTCTGCTC TCTCTGGG GGTGCTGG TGCCGGGTG TCCGGGCTT  
CCCCGCGTG CTGGGCTTC TGCGGTCTT GGGTGTCT TGGCCCGCT CGTGTGCG TCCGTGCGG GTCGCGGCG  
TGTCCCTC CTGGGTGCG GCGGGCTG TCCTGGCTT TTGCTCTC CTGGCGTCT TGGGTGCBG GGCCCTCT  
GCTGCGCTG GCGCTGCT TGCTGCGT TGTGGGGG CCGGGGTGG TGGCCCTG TTGCCGACG ACCCGGGGC  
50 GACCCAGGC TCGGGGGCT GTGTCTGC GCTGTGGG TGGGCCCT CTGGGGCTG GGTTCCTG TCGGCTGG  
CGCTGGCTG TTGGGTGCG GGGCGGGG GCGGGGGG CGCTGTCTG GGGCTGGG GTGCTGTG CTGCGGTTG  
CCCCGTTGG TCGCGCGCT CTGCTGCCG TGTGTGGT GTGCCCCG CCGTTTCTT GGGTCCGCG TGGGTGCT  
CGGTCTCTG TGCCGCTGT GCCTGTCT TCCGGCGTG GCGGCTGGT GTCCGCCCC CCTGGCCT CTGCTGGG  
TCTGGCTGT TGCCGGTGC CTGGCGCG GTCTCTTCC TGTGGCTCT GGGCCCGG GGTCTGGG GTCTGTGT  
CGCTCTGT CTGTCCGCG GCTCTTCC TCTCCGCG CCGCGCTC CCGCCGCT GTCGCGCTG CCGGCTCT  
55 TCTGGCGG TGTCTGGG GCGGCTTG GCGTCCGT TGGGCTGC TCTGGGCTT CCGGCTCT GCTGGGCG  
TCTTCCG CTGTCTGT GGCCTCTG GCGGCTCT GCGCTCGG GTCTGTGT CCGCGGCT GTGGGCGG  
CGGTGGGCG GCGTGGGCG CCGCGGGT CTCCGGCTG CCTTCTCC CCGGGGTG CCGCTCTG CTGTCTCT  
GGCTCTCT CCTCTCT GGTGGGTG TGGGTGCGG GTCTCCGG CTGCCCCG GCTGTGGG GTCTGCGG  
CTTGGGTTG TGTGGGCC CGCTGTGT GCGTCCGT CCGGCTGCG GCGCTCTG CCTCTGGT GCGGCGGG  
60 CTGGTCTG CGTTTGTCT CTCTCTG-3' (FRAG. NO:1892) (SEQ. ID NO:1903)  
5'-GCGGGGCG-3' (FRAG. NO:1893) (SEQ. ID NO:1904)  
5'-CGGGGGCG-3' (FRAG. NO:1894) (SEQ. ID NO:1905)

5'-GCGCGGCGGGC-3' (FRAG. NO:1895) (SEQ. ID NO: 1906)  
 5'-CTGTGCGTCCGCTCTGCTGG (FRAG. NO:1390)(SEQ. ID NO:1400)  
 GGGGCGGGGTGGCTGGGCCCTGCTTGCCGC (FRAG. NO:1391)(SEQ. ID NO:1401)  
 ACGACCCCGGGCCGACCCGAG (FRAG. NO:1392)(SEQ. ID NO:1402)  
 5 GCTCGGGGGGCTGTGTCTGGCGCTGGTGGG (FRAG. NO:1393)(SEQ. ID NO:1403)  
 CTTGGGCCCTCTGGGGGCTGGGTT (FRAG. NO:1394)(SEQ. ID NO:1404)  
 TCCTGCTGCGCCTGGGCGCTG (FRAG. NO:1395)(SEQ. ID NO:1405)  
 GCGTCTGGGGTGC (FRAG. NO:1396)(SEQ. ID NO:1406)  
 GGGGCGGGGGGCCGGGGG (FRAG. NO:1397)(SEQ. ID NO:1407)  
 10 GCCGCTGTTCTGTTGGCCTGGG (FRAG. NO:1398)(SEQ. ID NO:1408)  
 GGTGCTGTGGCTGCC (FRAG. NO:1399)(SEQ. ID NO:1409)  
 GGTGCCCCGGTTGGTGGC (FRAG. NO:1400)(SEQ. ID NO:1410)  
 GCCGCTCTGCTGCCGT (FRAG. NO:1401)(SEQ. ID NO:1411)  
 CGTTGGCTGGTCCCCCGC (FRAG. NO:1402)(SEQ. ID NO:1412)  
 15 CCGTTTCTGGGGTCC (FRAG. NO:1403)(SEQ. ID NO:1413)  
 GCGTGGGTGCTCC (FRAG. NO:1404)(SEQ. ID NO:1414)  
 GGTTCCTCTGCCG (FRAG. NO:1405)(SEQ. ID NO:1415)  
 CTGCTGCCTTGTCTTCC (FRAG. NO:1406)(SEQ. ID NO:1416)  
 GGCGTGGCGCGGTGGTGGTCC (FRAG. NO:1407)(SEQ. ID NO:1417)  
 20 GGGGGGCTGGCCTTCTGCTC (FRAG. NO:1408)(SEQ. ID NO:1418)  
 GGGGCTGGCTGGT (FRAG. NO:1409)(SEQ. ID NO:1419)  
 TGCCGGTGCCCTTGGCGGC (FRAG. NO:1410)(SEQ. ID NO:1420)  
 GGTCTTCTCTGGTG (FRAG. NO:1411)(SEQ. ID NO:1421)  
 GCTGTTGGGCGCGGTCTCGG (FRAG. NO:1412)(SEQ. ID NO:1422)  
 25 GCGTCTCGTGTCC (FRAG. NO:1413)(SEQ. ID NO:1423)  
 CTCTGTGCTGTTCCGGCCG (FRAG. NO:1414)(SEQ. ID NO:1424)  
 CTCCTTCTCTTCCGCCGC (FRAG. NO:1415)(SEQ. ID NO:1425)  
 GCCGCTCCCCGCC (FRAG. NO:1416)(SEQ. ID NO:1426)  
 GCTCGTCGCCCTGGCCC (FRAG. NO:1417)(SEQ. ID NO:1427)  
 30 GGCCTCTCTGGCCGC (FRAG. NO:1418)(SEQ. ID NO:1428)  
 TGTCTGGGCGCGGCTTGGC (FRAG. NO:1419)(SEQ. ID NO:1429)  
 GCTCGTTTGGGGCTG (FRAG. NO:1420)(SEQ. ID NO:1430)  
 CCTCTGGCGCTTCC (FRAG. NO:1421)(SEQ. ID NO:1431)  
 GGCCCTCGGCTGGGCGCTC (FRAG. NO:1422)(SEQ. ID NO:1432)  
 35 TCTTCCGCTGTGC (FRAG. NO:1423)(SEQ. ID NO:1433)  
 TGGTGGCCCTCGTGG (FRAG. NO:1424)(SEQ. ID NO:1434)  
 GCCCTCTGGCCTCCGGTGTCC (FRAG. NO:1425)(SEQ. ID NO:1435)  
 TGTGTCCCCCGGCTGGT (FRAG. NO:1426)(SEQ. ID NO:1436)  
 GGCCGGGCGGTTGGGCGGGC (FRAG. NO:1427)(SEQ. ID NO:1437)  
 40 GTGGGCGCGGCGGCTCTCC (FRAG. NO:1428)(SEQ. ID NO:1438)  
 GGGCTGCCCTTCTCC (FRAG. NO:1429)(SEQ. ID NO:1439)  
 GCCGGGGTCCCGC (FRAG. NO:1430)(SEQ. ID NO:1440)  
 GCTCTGTGTTCCTGGGCTTCTGCC (FRAG. NO:1431)(SEQ. ID NO:1441)  
 TCTCTCTGGGTGGGTGCTGGGTGCCG (FRAG. NO:1432)(SEQ. ID NO:1442)  
 45 GGGTCTCCGGGCTTG (FRAG. NO:1433)(SEQ. ID NO:1443)  
 CCCCAGCTGTGGGCGTTCTGC (FRAG. NO:1434)(SEQ. ID NO:1444)  
 GGTCTTGGGGTTGTC (FRAG. NO:1435)(SEQ. ID NO:1445)  
 TGTGGCCCCGCTCG (FRAG. NO:1436)(SEQ. ID NO:1446)  
 TGTGCCCCCTCCGTCGCC (FRAG. NO:1437)(SEQ. ID NO:1447)  
 50 CGTCGCCCCGCTCGTCC (FRAG. NO:1438)(SEQ. ID NO:1448)  
 CCTCTGGGTGCGC (FRAG. NO:1439)(SEQ. ID NO:1449)  
 GGCGGGCTGGTCT (FRAG. NO:1440)(SEQ. ID NO:1450)  
 GGCGTTTGTCTCTCTCTGG (FRAG. NO:1441)(SEQ. ID NO:1451)  
 5'-GCGTCTTGGGGTGCBBGGCCCTCTGCTGCGCTGGGCGTG-3' (FRAG. NO:1896) (SEQ. ID NO: 1907)

# 55 **Inducible Nitric Oxide Synthase Antisense Oligonucleotide Fragments**

5'-CTGCCCBGT TTTGTBCTCT CBCBTGCCGT GGGGBGGGCTGCTGCTT CCCCAGGGTT TCTGCTGCTT GCTGCTTCTT  
 TCCCGTCTCC CTCTTTTCCC GTCTCTTTT TGCTCTTTT GGTCTCTGTT GTTCTGCCC TGCTGGTGG CGGCTTGTGC  
 GTTCTCTCT TCTTCTTTT GGTCTCCGCT TCTGCTCTG CTTTTCCTG TCTCTGTCC GCCGTCTCT CTCGCGCTC  
 CTCTGCCCT GTGCTTTT CCTCGGGTGG TGCGGGTCCC GGTGCTCCC CGGCGGGCCG GCTGGTGGC TGGGCTGTG  
 60 TGTGGGGT TGGGGCGCT GGGTGGGGG TGTGGTGGG TCTTCTGTT GCTGTGGGG TGTGGGTGTC TCTGTGGGC  
 TGTGCTGGT CTGGGGCTT CCTCCTTGT GCTGGGTGG CCTCCCCG CCCCCTCTG GGCCGGTGGC CTGGCTCCTT  
 GTGGGCGCT CTGGCTCTT CCTGTCTT CTGCGCTCG TGGCTGCTG GCTGC-3' (FRAG. NO:1897) (SEQ. ID NO: 1908)

- 5'-CCCCGGGG-3' (FRAG. NO:1898) (SEQ. ID NO: 1909)  
 5'-GGGGCCCGCTGGG-3' (FRAG. NO:1899) (SEQ. ID NO:1910)  
 5'-GGGGGTGTGG-3' (FRAG. NO:1900) (SEQ. ID NO: 1911)  
 5'-CTGCCTCCCCGGGGT-3' (FRAG. NO:1442)(SEQ. ID NO:1452)  
 5'-TTCTGCTGCTTGTG-3' (FRAG. NO:1443)(SEQ. ID NO:1453)  
 5'-CTTCTTTCCCGTCTCC-3' (FRAG. NO:1444)(SEQ. ID NO:1454)  
 5'-CTTCTTTCCCGTCTCC-3' (FRAG. NO:1445)(SEQ. ID NO:1455)  
 5'-TTTTGCCTCTTTG-3' (FRAG. NO:1446)(SEQ. ID NO:1456)  
 5'-GGTTCCTGTTGTTTCT-3' (FRAG. NO:1447)(SEQ. ID NO:1457)  
 5'-GGCCTGCTTGGTGGCG-3' (FRAG. NO:1448)(SEQ. ID NO:1458)  
 5'-GCTTGTGCGTTTCC-3' (FRAG. NO:1449)(SEQ. ID NO:1459)  
 5'-TCTCTCTTCTTGGGTCTCCGCTTCTCGTCTGCC-3' (FRAG. NO:1450)(SEQ. ID NO:1460)  
 5'-TTTTCCTGTCTGTGCGC-3' (FRAG. NO:1451)(SEQ. ID NO:1461)  
 5'-GCCGTTCTCTCC-3' (FRAG. NO:1452)(SEQ. ID NO:1462)  
 5'-GGCGTCTCTCGCC-3' (FRAG. NO:1453)(SEQ. ID NO:1463)  
 5'-TGTGCTGTTTGCCTCGG-3' (FRAG. NO:1454)(SEQ. ID NO:1464)  
 5'-GTGTGCGGGTCCC-3' (FRAG. NO:1455)(SEQ. ID NO:1465)  
 5'-GGTGCTCCCCCGG-3' (FRAG. NO:1456)(SEQ. ID NO:1466)  
 5'-GGGCGGCTGTTGCTGGGC-3' (FRAG. NO:1457)(SEQ. ID NO:1467)  
 5'-CTGTCTGTGGGTGTGGGCC-3' (FRAG. NO:1458)(SEQ. ID NO:1468)  
 5'-GCTGGGTGTGGGGTGTGGTG-3' (FRAG. NO:1459)(SEQ. ID NO:1469)  
 5'-GGCTTCTGTGGCC-3' (FRAG. NO:1460)(SEQ. ID NO:1470)  
 5'-TGTGGGGCTGTTGGTG-3' (FRAG. NO:1461)(SEQ. ID NO:1471)  
 5'-TCTCTGTGGCGTGTG-3' (FRAG. NO:1462)(SEQ. ID NO:1472)  
 5'-CTGGGTCTTGGGGCTTC-3' (FRAG. NO:1463)(SEQ. ID NO:1473)  
 5'-CTCCCTGTGCTGGG-3' (FRAG. NO:1464)(SEQ. ID NO:1474)  
 5'-TGCGGCCTCCCCGC-3' (FRAG. NO:1465)(SEQ. ID NO:1475)  
 5'-CCCCCTTCTGGGC-3' (FRAG. NO:1466)(SEQ. ID NO:1476)  
 5'-GGTGGCCTGGCTCCTTGTGG-3' (FRAG. NO:1467)(SEQ. ID NO:1477)  
 5'-GCCGTTCTGGCTCTTG-3' (FRAG. NO:1468)(SEQ. ID NO:1478)  
 5'-CCCTGTCTTCTTCGCTCGT-3' (FRAG. NO:1469)(SEQ. ID NO:1479)  
 5'-GGCTGCTGGGCTGC-3' (FRAG. NO:1470)(SEQ. ID NO:1480)  
 5'-CTGCCCBGTTTTTGTCTCCTCCTGCGGGBGGBCBBTGG-3' (FRAG. NO:1901) (SEQ. ID NO: 1912)

### NF- $\kappa$ B Antisense Oligonucleotide Fragments

- 5'-CGGCCCTTCT CACTGGAGGC ACCGGGACGT CCTCCATGGG AGGGTTGGGC TTGGCCGGGG CTGCCCGGTG CCTCTCTTTC  
 GCTGGTCCCT CGTGTCTTT GGGCCCCG TCCCGTGTCT CGGCCTCCGT GTTCTTTGGC CTCTTGCTCC GCCTGCTGTC  
 TTGTCCCGTC CCTCTCTGCG TTGCGTTTCC CTCTTCTTTC TCTTCCAGGC CTTCCTCCGC TTCCGCTGTG GGGGCCCGCG  
 CCGGGGGGGC GCTGGGCTCC GCGGCTTCT CCCCCTGCTG GGGGTCTGG TCTCCGGGGC CTGCGGCTCG CGGGCTCGGG  
 GCTGCGTGG CCGCGCGCG GGTCCGCGGT GGGTGGCGCT GTCCCGCCGT GGTGTGTCTC CGTTCCTGCT CTGCGCCGTC  
 CTGGTCTGCC CGTGGGGTCC TGGGCGTGGT GGGGGGCGTC TGGTGCCTCG TCTGCCCCGT GGGGCTTCGG GCTCGGGGCT  
 GTTCGTCCCC CTTGCCGCTC TGTGGCCTCC GGGGCTCTC GTTTTCGCTG CTTCGGGTGT CCTTCTCGGC GTGTGGCCCC  
 GGGTCCCCGC CTTGCTGGG TGGGCGGGT CGTGCCTG GGTCTCTGGC CCGTCTGGT GTCTGTCCGT GCTTGTCTCG  
 GGTCTCTGGC CTCTGTGCTG GGCCTTCTC TGCTCCTG TCCGCCCTCC TGGTGGCTCG GCTGGGGGTG CCCGTGCGGG  
 GGTGGGTGTG GGGTGTTC GGGGTCTCC CCTTCCC-3' (FRAG. NO:1902) (SEQ. ID NO:1913)  
 5'-GGGCGGGGTCCG-3' (FRAG. NO:1903) (SEQ. ID NO:1914)  
 5'-GCGCCGTCC-3' (FRAG. NO:1904) (SEQ. ID NO:1915)  
 5'-GGGCGTGGTGG-3' (FRAG. NO:1905) (SEQ. ID NO:1916)  
 5'-GTTGGGCTTGGCCGGGG-3' (FRAG. NO:1471)(SEQ. ID NO:1481)  
 5'-CTGCCCGTGCCTCC-3' (FRAG. NO:1472)(SEQ. ID NO:1482)  
 5'-TCTTGGCTGGTCCCTCGT-3' (FRAG. NO:1473)(SEQ. ID NO:1483)  
 5'-TGTCTTGGGCCCC-3' (FRAG. NO:1474)(SEQ. ID NO:1484)  
 5'-GCTCCCGTGTCTCGGCTCCGT-3' (FRAG. NO:1475)(SEQ. ID NO:1485)  
 5'-GTTCTTTGGCCTTTGCTCC-3' (FRAG. NO:1476)(SEQ. ID NO:1486)  
 5'-GCCTGCTGTCTTGTCC-3' (FRAG. NO:1477)(SEQ. ID NO:1487)  
 5'-CGTCCCCCTCTCGCTTGGGTTTC-3' (FRAG. NO:1478)(SEQ. ID NO:1488)  
 5'-CCTCTTCTTGTCTTCCA-3' (FRAG. NO:1479)(SEQ. ID NO:1489)  
 5'-GGCCTTCTCCGCTTCCGCTGC-3' (FRAG. NO:1480)(SEQ. ID NO:1490)  
 5'-TGGGGCCCGCGCCG-3' (FRAG. NO:1481)(SEQ. ID NO:1491)  
 5'-GGGGGCGCTCGGCTCCGCGGCTTCTCCCCGG-3' (FRAG. NO:1482)(SEQ. ID NO:1492)  
 5'-CTGGGGGCTCCTTG-3' (FRAG. NO:1483)(SEQ. ID NO:1493)  
 5'-TCTCCGGGCTCGGCTCGC-3' (FRAG. NO:1484)(SEQ. ID NO:1494)  
 5'-GGGCTCGGGCTGCTGCGCC-3' (FRAG. NO:1485)(SEQ. ID NO:1495)

- 5'-GCGCGCGGCGTCCGCGGTG-3' (FRAG. NO:1486)(SEQ. ID NO:1496)  
 5'-GGTGGCGCTGTCCCGCC-3' (FRAG. NO:1487)(SEQ. ID NO:1497)  
 5'-GTGGTGTGTCTCCGTTCTCTGCTGCGCGTC-3' (FRAG. NO:1488)(SEQ. ID NO:1498)  
 5'-CTGGTCTGCCCGTGG-3' (FRAG. NO:1489)(SEQ. ID NO:1499)  
 5'-GGTCTGGGCGTGGTGG-3' (FRAG. NO:1490)(SEQ. ID NO:1500)  
 5'-GGGGCGTCTGGTGC-3' (FRAG. NO:1491)(SEQ. ID NO:1501)  
 5'-CTCGTCTGCCCGTG-3' (FRAG. NO:1492)(SEQ. ID NO:1502)  
 5'-GGGCTTCGGGCTCGG-3' (FRAG. NO:1493)(SEQ. ID NO:1503)  
 5'-GGCTGTCTGCCCCCTGCCGCTCTGTGGCCTCC-3' (FRAG. NO:1494)(SEQ. ID NO:1504)  
 5'-GGGGCTCCTCGTTTC-3' (FRAG. NO:1495)(SEQ. ID NO:1505)  
 5'-GCTGTTTCGGGTGTCTTCTC-3' (FRAG. NO:1496)(SEQ. ID NO:1506)  
 5'-GGCGTGTGGCCCCGG-3' (FRAG. NO:1497)(SEQ. ID NO:1507)  
 5'-GTCCCGGCCCTGCTGGGCTGGGCGGGTGC-3' (FRAG. NO:1498)(SEQ. ID NO:1508)  
 5'-GCTGCCCTGGGCTTCTGGCCCGTCT-3' (FRAG. NO:1499)(SEQ. ID NO:1509)  
 5'-GGTTGTCTGTCGGT-3' (FRAG. NO:1500)(SEQ. ID NO:1510)  
 5'-GCTTGTCTCGGGTTTCTGG-3' (FRAG. NO:1501)(SEQ. ID NO:1511)  
 5'-CCTCTGTGCTGGGC-3' (FRAG. NO:1502)(SEQ. ID NO:1512)  
 5'-GCTTCTCTGCCTCCTGCTCC-3' (FRAG. NO:1503)(SEQ. ID NO:1513)  
 5'-GCCCTCCTGGTGGCTC-3' (FRAG. NO:1504)(SEQ. ID NO:1514)  
 5'-GGCTGGGGGTGCCCGTGCG-3' (FRAG. NO:1505)(SEQ. ID NO:1515)  
 5'-GGGGTGGGTGTGGGGTGT-3' (FRAG. NO:1506)(SEQ. ID NO:1516)  
 5'-TTCGGGGTCTCCCTTCC-3' (FRAG. NO:1507)(SEQ. ID NO:1517)  
 5'-CGGCCCTTCTCACTGGAGGCACCGGCGAGTCTCCATGGGAGG-3' (FRAG. NO:1906)(SEQ. ID NO:1917)

#### **Human Major Basic Protein Anti-sense Oligonucleotide Fragments**

- 5'-GTT TCA TCT TGG CTT TAT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC  
 CCT GCC GTG TTG TCT GTG GGT GTC GTT TCG CTC TTG TTG CCC TGG GCC CTT CCC TGC TGG GGG GGA GTT TCA TCT  
 TGG GTT TCB TCT TGG CTT TBT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC  
 CCT GCC GTG TTG TCT GTG GGT GTC GTT TCG CTC TTG TTG CCC TGG GCC CTT CCC TGC TGG GGG GGB GTT TCB TCT  
 TGG-3' (FRAG. ID:1907) (SEQ. ID NO:1918)  
 5'-GGG GGA GTT-3' (FRAG. ID:1908) (SEQ. ID NO:1919)  
 5'-G CCC TGG GCC C-3' (FRAG. ID:1909) (SEQ. ID NO:1920)  
 5'-GTT TCA TCT TGG CTT TAT CC-3' (FRAG. NO:1508) (SEQ. ID NO:1518)  
 5'-TCT CCC CTT GTT CCT CCC C-3' (FRAG. NO:1509) (SEQ. ID NO:1519)  
 5'-TCT CCT GCT CTG GRG TCT CCT C-3' (FRAG. NO:1510) (SEQ. ID NO:1520)  
 5'-TTC CCT CCC TCC CCT GCC-3' (FRAG. NO:1511) (SEQ. ID NO:1521)  
 5'-GTG TTG TCT GTG GGT GTC C-3' (FRAG. NO:1512) (SEQ. ID NO:1522)  
 5'-GTT TCG CTC TTG TTG CCC-3' (FRAG. NO:1513) (SEQ. ID NO:1523)  
 5'-TGG GCC CTT CCC TGC TGG-3' (FRAG. NO:1514) (SEQ. ID NO:1524)  
 5'-GGG GGA GTT TCA TCT TGG-3' (FRAG. NO:1515) (SEQ. ID NO:1525)  
 5'-GTT TCA TCT TGG CTT TAT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC  
 CCT GCC GTG TTG TCT GTG GGT GTC GTT TCG CTC TTG TTG CCC TGG GCC CTT CCC TGC TGG GGG GGA GTT TCA TCT  
 TGG-3' (FRAG. ID:1910) (SEQ. ID NO:1921)  
 5'-GTT TCB TCT TGG CTT TBT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC  
 CCT GCC GTG TTG TCT GTG GGT GTC GTT TCG CTC TTG TTG CCC TGG GCC CTT CCC TGC TGG GGG GGB GTT TCB TCT  
 TGG-3' (FRAG. ID:1911) (SEQ. ID NO:1922)

#### **Human Eosinophil Major Basic Protein Fragments**

- 5'-GGG GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1516) (SEQ. ID NO:1526)  
 5'-GGG GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1517) (SEQ. ID NO:1527)  
 5'-GGG GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1518) (SEQ. ID NO:1528)  
 5'-GGG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1519) (SEQ. ID NO:1529)  
 5'-GGG GGB GTT TCB TCT TGG-3' (FRAG. NO:1520) (SEQ. ID NO:1530)  
 5'-GGG GGB GTT TCB TCT TG-3' (FRAG. NO:1521) (SEQ. ID NO:1531)  
 5'-GGG GGB GTT TCB TCT T-3' (FRAG. NO:1522) (SEQ. ID NO:1532)  
 5'-GGG GGB GTT TCB TCT-3' (FRAG. NO:1523) (SEQ. ID NO:1533)  
 5'-GGG GGB GTT TCB TC-3' (FRAG. NO:1524) (SEQ. ID NO:1534)  
 5'-GGG GGB GTT TCB T-3' (FRAG. NO:1525) (SEQ. ID NO:1535)  
 5'-GGG GGB GTT TCB-3' (FRAG. NO:1526) (SEQ. ID NO:1536)  
 5'-GG GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1527) (SEQ. ID NO:1537)  
 5'-GG GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1528) (SEQ. ID NO:1538)  
 5'-GG GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1529) (SEQ. ID NO:1539)

- 5'-GG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1530)(SEQ. ID NO:1540)  
 5'-GG GGB GTT TCB TCT TGG-3' (FRAG. NO:1531)(SEQ. ID NO:1541)  
 5'-GG GGB GTT TCB TCT TG-3' (FRAG. NO:1532)(SEQ. ID NO:1542)  
 5'-GG GGB GTT TCB TCT T-3' (FRAG. NO:1533)(SEQ. ID NO:1543)  
 5 5'-GG GGB GTT TCB TCT-3' (FRAG. NO:1534)(SEQ. ID NO:1544)  
 5'-GG GGB GTT TCB TC-3' (FRAG. NO:1535)(SEQ. ID NO:1545)  
 5'-GG GGB GTT TCB T-3' (FRAG. NO:1536)(SEQ. ID NO:1546)  
 5'-G GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1537)(SEQ. ID NO:1547)  
 5'-G GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1538)(SEQ. ID NO:1548)  
 10 5'-G GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1539)(SEQ. ID NO:1549)  
 5'-G GGB GTT TCB TCT TGG C-3' (FRAG. NO:1540)(SEQ. ID NO:1550)  
 5'-G GGB GTT TCB TCT TGG-3' (FRAG. NO:1541)(SEQ. ID NO:1551)  
 5'-G GGB GTT TCB TCT TG-3' (FRAG. NO:1542)(SEQ. ID NO:1552)  
 5'-G GGB GTT TCB TCT T-3' (FRAG. NO:1543)(SEQ. ID NO:1553)  
 15 5'-G GGB GTT TCB TCT-3' (FRAG. NO:1544)(SEQ. ID NO:1554)  
 5'-G GGB GTT TCB TC-3' (FRAG. NO:1545)(SEQ. ID NO:1555)  
 5'-GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1546)(SEQ. ID NO:1556)  
 5'-GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1547)(SEQ. ID NO:1557)  
 20 5'-GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1548)(SEQ. ID NO:1558)  
 5'-GGB GTT TCB TCT TGG C-3' (FRAG. NO:1549)(SEQ. ID NO:1559)  
 5'-GGB GTT TCB TCT TGG-3' (FRAG. NO:1550)(SEQ. ID NO:1560)  
 5'-GGB GTT TCB TCT TG-3' (FRAG. NO:1551)(SEQ. ID NO:1561)  
 5'-GGB GTT TCB TCT T-3' (FRAG. NO:1552)(SEQ. ID NO:1562)  
 25 5'-GGB GTT TCB TCT-3' (FRAG. NO:1553)(SEQ. ID NO:1563)  
 5'-GB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1554)(SEQ. ID NO:1564)  
 5'-GB GTT TCB TCT TGG CTT-3' (FRAG. NO:1555)(SEQ. ID NO:1565)  
 5'-GB GTT TCB TCT TGG CT-3' (FRAG. NO:1556)(SEQ. ID NO:1566)  
 5'-GB GTT TCB TCT TGG C-3' (FRAG. NO:1557)(SEQ. ID NO:1567)  
 5'-GB GTT TCB TCT TGG-3' (FRAG. NO:1558)(SEQ. ID NO:1568)  
 30 5'-GB GTT TCB TCT TG-3' (FRAG. NO:1559)(SEQ. ID NO:1569)  
 5'-GB GTT TCB TCT T-3' (FRAG. NO:1560)(SEQ. ID NO:1570)  
 5'-B GTT TCB TCT TGG CTT T-3' (FRAG. NO:1561)(SEQ. ID NO:1571)  
 5'-B GTT TCB TCT TGG CTT-3' (FRAG. NO:1562)(SEQ. ID NO:1572)  
 35 5'-B GTT TCB TCT TGG CTT-3' (FRAG. NO:1563)(SEQ. ID NO:1573)  
 5'-B GTT TCB TCT TGG CT-3' (FRAG. NO:1564)(SEQ. ID NO:1574)  
 5'-B GTT TCB TCT TGG C-3' (FRAG. NO:1565)(SEQ. ID NO:1575)  
 5'-B GTT TCB TCT TGG-3' (FRAG. NO:1566)(SEQ. ID NO:1576)  
 5'-B GTT TCB TCT TG-3' (FRAG. NO:1567)(SEQ. ID NO:1577)  
 40 5'-GTT TCB TCT TGG CTT T-3' (FRAG. NO:1568)(SEQ. ID NO:1578)  
 5'-GTT TCB TCT TGG CTT-3' (FRAG. NO:1569)(SEQ. ID NO:1579)  
 5'-GTT TCB TCT TGG CT-3' (FRAG. NO:1570)(SEQ. ID NO:1580)  
 5'-GTT TCB TCT TGG C-3' (FRAG. NO:1571)(SEQ. ID NO:1581)  
 5'-GTT TCB TCT TGG-3' (FRAG. NO:1572)(SEQ. ID NO:1582)  
 45 5'-TT TCB TCT TGG CTT T-3' (FRAG. NO:1573)(SEQ. ID NO:1583)  
 5'-TT TCB TCT TGG CTT-3' (FRAG. NO:1574)(SEQ. ID NO:1584)  
 5'-TT TCB TCT TGG CT-3' (FRAG. NO:1575)(SEQ. ID NO:1585)  
 5'-TT TCB TCT TGG C-3' (FRAG. NO:1576)(SEQ. ID NO:1586)  
 5'-T TCB TCT TGG CTT T-3' (FRAG. NO:1577)(SEQ. ID NO:1587)  
 50 5'-T TCB TCT TGG CTT-3' (FRAG. NO:1578)(SEQ. ID NO:1588)  
 5'-T TCB TCT TGG CT-3' (FRAG. NO:1579)(SEQ. ID NO:1589)  
 5'-TCB TCT TGG CTT T-3' (FRAG. NO:1580)(SEQ. ID NO:1590)  
 5'-TCB TCT TGG CTT-3' (FRAG. NO:1581)(SEQ. ID NO:1591)  
 5'-GGG GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1582)(SEQ. ID NO:1592)  
 55 5'-GG GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1583)(SEQ. ID NO:1593)  
 5'-G GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1584)(SEQ. ID NO:1594)  
 5'-GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1585)(SEQ. ID NO:1595)  
 5'-GB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1586)(SEQ. ID NO:1596)  
 5'-B GTT TCB TCT TGG CTT T-3' (FRAG. NO:1587)(SEQ. ID NO:1597)  
 5'-GTT TCB TCT TGG CTT T-3' (FRAG. NO:1588)(SEQ. ID NO:1598)  
 60 5'-TT TCB TCT TGG CTT T-3' (FRAG. NO:1589)(SEQ. ID NO:1599)  
 5'-T TCB TCT TGG CTT T-3' (FRAG. NO:1590)(SEQ. ID NO:1600)  
 5'-GTT TCB TCT TGG CTT T-3' (FRAG. NO:1591)(SEQ. ID NO:1601)  
 5'-CB TCT TGG CTT T-3' (FRAG. NO:1592)(SEQ. ID NO:1602)  
 5'-GGG GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1593)(SEQ. ID NO:1603)

- 5'-GG GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1594)(SEQ. ID NO:1604)  
 5'-G GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1595)(SEQ. ID NO:1605)  
 5'-GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1596)(SEQ. ID NO:1606)  
 5'-GB GTT TCB TCT TGG CTT-3' (FRAG. NO:1597)(SEQ. ID NO:1607)  
 5 5'-B GTT TCB TCT TGG CTT-3' (FRAG. NO:1598)(SEQ. ID NO:1608)  
 5'-GTT TCB TCT TGG CTT-3' (FRAG. NO:1599)(SEQ. ID NO:1609)  
 5'-TT TCB TCT TGG CTT-3' (FRAG. NO:1600)(SEQ. ID NO:1610)  
 5'-T TCB TCT TGG CTT-3' (FRAG. NO:1601)(SEQ. ID NO:1611)  
 5'-TCB TCT TGG CTT-3' (FRAG. NO:1602)(SEQ. ID NO:1612)  
 10 5'-GGG GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1603)(SEQ. ID NO:1613)  
 5'-GG GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1604)(SEQ. ID NO:1614)  
 5'-G GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1605)(SEQ. ID NO:1615)  
 5'-GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1606)(SEQ. ID NO:1616)  
 5'-GB GTT TCB TCT TGG CT-3' (FRAG. NO:1607)(SEQ. ID NO:1617)  
 15 5'-B GTT TCB TCT TGG CT-3' (FRAG. NO:1608)(SEQ. ID NO:1618)  
 5'-GTT TCB TCT TGG CT-3' (FRAG. NO:1609)(SEQ. ID NO:1619)  
 5'-TT TCB TCT TGG CT-3' (FRAG. NO:1610)(SEQ. ID NO:1620)  
 5'-T TCB TCT TGG CT-3' (FRAG. NO:1611)(SEQ. ID NO:1621)  
 5'-GGG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1612)(SEQ. ID NO:1622)  
 20 5'-GG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1613)(SEQ. ID NO:1623)  
 5'-G GGB GTT TCB TCT TGG C-3' (FRAG. NO:1614)(SEQ. ID NO:1624)  
 5'-GGB GTT TCB TCT TGG C-3' (FRAG. NO:1615)(SEQ. ID NO:1625)  
 5'-GB GTT TCB TCT TGG C-3' (FRAG. NO:1616)(SEQ. ID NO:1626)  
 5'-B GTT TCB TCT TGG C-3' (FRAG. NO:1617)(SEQ. ID NO:1627)  
 25 5'-GTT TCB TCT TGG C-3' (FRAG. NO:1618)(SEQ. ID NO:1628)  
 5'-TT TCB TCT TGG C-3' (FRAG. NO:1619)(SEQ. ID NO:1629)  
 5'-GGG GGB GTT TCB TCT TGG-3' (FRAG. NO:1620)(SEQ. ID NO:1630)  
 5'-GG GGB GTT TCB TCT TGG-3' (FRAG. NO:1621)(SEQ. ID NO:1631)  
 5'-G GGB GTT TCB TCT TGG-3' (FRAG. NO:1622)(SEQ. ID NO:1632)  
 30 5'-GGB GTT TCB TCT TGG-3' (FRAG. NO:1623)(SEQ. ID NO:1633)  
 5'-GB GTT TCB TCT TGG-3' (FRAG. NO:1624)(SEQ. ID NO:1634)  
 5'-B GTT TCB TCT TGG-3' (FRAG. NO:1625)(SEQ. ID NO:1635)  
 5'-GTT TCB TCT TGG-3' (FRAG. NO:1626)(SEQ. ID NO:1636)  
 5'-GGG GGB GTT TCB TCT TG-3' (FRAG. NO:1627)(SEQ. ID NO:1637)  
 35 5'-GG GGB GTT TCB TCT TG-3' (FRAG. NO:1628)(SEQ. ID NO:1638)  
 5'-G GGB GTT TCB TCT TG-3' (FRAG. NO:1629)(SEQ. ID NO:1639)  
 5'-GGB GTT TCB TCT TG-3' (FRAG. NO:1630)(SEQ. ID NO:1640)  
 5'-GB GTT TCB TCT TG-3' (FRAG. NO:1631)(SEQ. ID NO:1641)  
 5'-B GTT TCB TCT TG-3' (FRAG. NO:1632)(SEQ. ID NO:1642)  
 40 5'-GGG GGB GTT TCB TCT T-3' (FRAG. NO:1633)(SEQ. ID NO:1643)  
 5'-GG GGB GTT TCB TCT T-3' (FRAG. NO:1634)(SEQ. ID NO:1644)  
 5'-G GGB GTT TCB TCT T-3' (FRAG. NO:1635)(SEQ. ID NO:1645)  
 5'-G GGB GTT TCB TCT T-3' (FRAG. NO:1636)(SEQ. ID NO:1646)  
 5'-GGB GTT TCB TCT T-3' (FRAG. NO:1637)(SEQ. ID NO:1647)  
 45 5'-GB GTT TCB TCT T-3' (FRAG. NO:1638)(SEQ. ID NO:1648)  
 5'-GGG GGB GTT TCB TCT-3' (FRAG. NO:1639)(SEQ. ID NO:1649)  
 5'-GG GGB GTT TCB TCT-3' (FRAG. NO:1640)(SEQ. ID NO:1650)  
 5'-G GGB GTT TCB TCT-3' (FRAG. NO:1641)(SEQ. ID NO:1651)  
 5'-GGB GTT TCB TCT-3' (FRAG. NO:1642)(SEQ. ID NO:1652)  
 50 5'-GGG GGB GTT TCB TC-3' (FRAG. NO:1643)(SEQ. ID NO:1653)  
 5'-GG GGB GTT TCB TC-3' (FRAG. NO:1644)(SEQ. ID NO:1654)  
 5'-G GGB GTT TCB TC-3' (FRAG. NO:1645)(SEQ. ID NO:1655)  
 5'-GGG GGB GTT TCB T-3' (FRAG. NO:1646)(SEQ. ID NO:1656)  
 5'-GG GGB GTT TCB T-3' (FRAG. NO:1647)(SEQ. ID NO:1657)  
 55 5'-GGG GGB GTT TCB-3' (FRAG. NO:1648)(SEQ. ID NO:1658)  
 5'-TCT CCC CTT GTT CCT CCC C-3' (FRAG. NO:1649)(SEQ. ID NO:1659)  
 5'-TCT CCT GCT CTG GTG TCT CCT C-3' (FRAG. NO:1650)(SEQ. ID NO:1660)  
 5'-TTC CCT CCC TCC CCT GCC-3' (FRAG. NO:1651)(SEQ. ID NO:1661)  
 5'-GTG TTG TCT GTG GGT GTC C-3' (FRAG. NO:1652)(SEQ. ID NO:1662)  
 60 5'-GTT TCG CTC TTG TTG CCC-3' (FRAG. NO:1653)(SEQ. ID NO:1663)  
 5'-TGG GCC CTT CCC TGC TGG-3' (FRAG. NO:1654)(SEQ. ID NO:1664)  
 5'-GGG GGB G-3' (FRAG. NO:1912)(SEQ. ID NO:1923)  
 5'-GTG GGT GTC C-3' (FRAG. NO:1913)(SEQ. ID NO:1924)

**BP-1 Antisense Oligonucleotide Fragments**

- 5'-CCGTGTTGTC BGTGGTGCTG CCCGTTTGBG GTBTGGCGCT CCBCCBBTTC CCTTTTCTCC TTGTTTCCG TTCTCTTG  
CGTCTGTTGGT T-3' (FRAG. NO:1914) (SEQ. ID NO:1925)  
5'-CCCGTTTGBGGTBTGGC-3' (FRAG. NO:1915) (SEQ. ID NO:1926)  
5'-GCTCCBCCBBTTCCTTTTCTCC-3' (FRAG. NO:1916) (SEQ. ID NO:1927)  
5'-TTGTTTCCGTTTCTCTTG-3' (FRAG. NO:1917) (SEQ. ID NO:1928)  
5'-CCGTCTGTGGT-3' (FRAG. NO:1918) (SEQ. ID NO:1929)  
5'-CCCGTTTGAAGTATGGC-3' (FRAG. NO:1919) (SEQ. ID NO:1930)  
5'-GCTCCBCCAATTCCCTTTTCTCC-3' (FRAG. NO:1920) (SEQ. ID NO:1931)

**10 C/EBP $\beta$  Antisense Oligonucleotide Fragments**

- 5'-GGGCCCCBGCCCCGCGCCTTTTCTBGCCCC GGCC-3' (FRAG. NO:1921) (SEQ. ID NO:1932)  
5'-GGGCCCCBGCCCCGCGCCTTTTCTBGCCCC GGC-3' (FRAG. NO:1922) (SEQ. ID NO:1933)  
5'-GGGCCCCB GCCCCGCGCCTTTTCTBGCCCCGG-3' (FRAG. NO:1923) (SEQ. ID NO:1934)  
5'-GGGCCCCBGCCCCGCGCCTTTTCTBGCCCCG-3' (FRAG. NO:1924) (SEQ. ID NO:1935)  
5'-GGGCCCCBGCCCCGCGCCTTTTCTBGCCCC-3' (FRAG. NO:1925) (SEQ. ID NO:1936)  
5'-GGGCCCCBGCCCCGCGCCTTTTCTBGCCCC-3' (FRAG. NO:1926) (SEQ. ID NO:1937)  
5'-GGGCCCCBGCCCCGCGCCTTTTCTBGCC-3' (FRAG. NO:1927) (SEQ. ID NO:1938)  
5'-GGGCCCCBGCCCCGCGCCTTTTCTBGC-3' (FRAG. NO:1928) (SEQ. ID NO:1939)  
5'-GGGCCCCBGCCCCGCGCCTTTTCTBG-3' (FRAG. NO:1929) (SEQ. ID NO:1940)  
5'-GGGCCCCBGCCCCGCGCCTTTTCTB-3' (FRAG. NO:1930) (SEQ. ID NO:1941)  
5'-GGGCCCCBGCCCCGCGCCTTTTCT-3' (FRAG. NO:1931) (SEQ. ID NO:1942)  
5'-GGGCCCCBGCCCCGCGCCTTTTC-3' (FRAG. NO:1932) (SEQ. ID NO:1943)  
5'-GGGCCCCBGCCCCGCGCCTTTT-3' (FRAG. NO:1933) (SEQ. ID NO:1944)  
5'-GGGCCCCBGCCCCGCGCCTTT-3' (FRAG. NO:1934) (SEQ. ID NO:1945)  
5'-GGGCCCCBGCCCCGCGCCTT-3' (FRAG. NO:1935) (SEQ. ID NO:1946)  
5'-GGGCCCCBGCCCCGCGCCT-3' (FRAG. NO:1936) (SEQ. ID NO:1947)  
5'-GGGCCCCBGCCCCGCGCC-3' (FRAG. NO:1937) (SEQ. ID NO:1948)  
5'-GGGCCCCBGCCCCGCGC-3' (FRAG. NO:1938) (SEQ. ID NO:1949)  
5'-GGGCCCCBGCCCCGCG-3' (FRAG. NO:1939) (SEQ. ID NO:1950)  
5'-GGGCCCCBGCCCCGC-3' (FRAG. NO:1940) (SEQ. ID NO:1951)  
5'-GGGCCCCBGCCCCG-3' (FRAG. NO:1941) (SEQ. ID NO:1952)  
5'-GGGCCCCBGCCCC-3' (FRAG. NO:1942) (SEQ. ID NO:1953)  
5'-GGGCCCCBGCCCC-3' (FRAG. NO:1943) (SEQ. ID NO:1954)  
5'-GGGCCCCBGCCCC-3' (FRAG. NO:1944) (SEQ. ID NO:1955)  
5'-GGCCCCBGCCCCGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1945) (SEQ. ID NO:1956)  
5'-GCCCBGCCCCGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1946) (SEQ. ID NO:1957)  
5'-CCCBGCCCCGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1947) (SEQ. ID NO:1958)  
5'-CCBGCCCCGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1948) (SEQ. ID NO:1959)  
5'-CBGCCCCGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1948) (SEQ. ID NO:1960)  
5'-BGCCCCGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1950) (SEQ. ID NO:1961)  
5'-GCCCGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1951) (SEQ. ID NO:1962)  
5'-CCCGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1952) (SEQ. ID NO:1963)  
5'-CCGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1953) (SEQ. ID NO:1964)  
5'-CCGCCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1954) (SEQ. ID NO:1965)  
5'-CGCGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1955) (SEQ. ID NO:1966)  
5'-GCCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1956) (SEQ. ID NO:1967)  
5'-CCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1957) (SEQ. ID NO:1968)  
5'-CGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1958) (SEQ. ID NO:1969)  
5'-GCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1959) (SEQ. ID NO:1970)  
5'-CCTTTTCTBGCCCCGGC-3' (FRAG. NO:1960) (SEQ. ID NO:1971)  
5'-CTTTTCTBGCCCCGGC-3' (FRAG. NO:1961) (SEQ. ID NO:1972)  
5'-TTTTCTBGCCCCGGC-3' (FRAG. NO:1962) (SEQ. ID NO:1973)  
5'-TTTCTBGCCCCGGC-3' (FRAG. NO:1963) (SEQ. ID NO:1974)  
5'-TTCTBGCCCCGGC-3' (FRAG. NO:1964) (SEQ. ID NO:1975)  
5'-TCTBGCCCCGGC-3' (FRAG. NO:1965) (SEQ. ID NO:1976)  
5'-CTBGCCCCGGC-3' (FRAG. NO:1966) (SEQ. ID NO:1977)  
5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1967) (SEQ. ID NO:1978)



5'-GCGBGGCTGTBCCTCGCTGGGCC-3' (FRAG. NO:1968) (SEQ. ID NO:1979)  
 5'-GCGBGGCTGTBCCTCGCTGGGC-3' (FRAG. NO:1969) (SEQ. ID NO:1980)  
 5'-GCGBGGCTGTBCCTCGCTGGG-3' (FRAG. NO:1970) (SEQ. ID NO:1981)  
 5'-GCGBGGCTGTBCCTCGCTGG-3' (FRAG. NO:1971) (SEQ. ID NO:1982)  
 5 5'-GCGBGGCTGTBCCTCGCTG-3' (FRAG. NO:1972) (SEQ. ID NO:1983)  
 5'-GCGBGGCTGTBCCTCGCT-3' (FRAG. NO:1973) (SEQ. ID NO:1984)  
 5'-GCGBGGCTGTBCCTCGC-3' (FRAG. NO:1974) (SEQ. ID NO:1985)  
 5'-GCGBGGCTGTBCCTCG-3' (FRAG. NO:1975) (SEQ. ID NO:1986)  
 5'-GCGBGGCTGTBCCTC-3' (FRAG. NO:1976) (SEQ. ID NO:1987)  
 10 5'-GCGBGGCTGTBCCT-3' (FRAG. NO:1977) (SEQ. ID NO:1988)  
 5'-GCGBGGCTGTBC-3' (FRAG. NO:1978) (SEQ. ID NO:1989)  
 5'-GCGBGGCTGTBC-3' (FRAG. NO:1979) (SEQ. ID NO:1990)  
 5'-GCGBGGCTGTB-3' (FRAG. NO:1980) (SEQ. ID NO:1991)  
 5'-GCGBGGCTGT-3' (FRAG. NO:1981) (SEQ. ID NO:1992)  
 15 5'-GCGBGGCTG-3' (FRAG. NO:1982) (SEQ. ID NO:1993)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1983) (SEQ. ID NO:1994)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1984) (SEQ. ID NO:1995)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1985) (SEQ. ID NO:1996)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1986) (SEQ. ID NO:1997)  
 20 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1987) (SEQ. ID NO:1998)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1988) (SEQ. ID NO:1999)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1989) (SEQ. ID NO:2000)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1990) (SEQ. ID NO:2001)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1991) (SEQ. ID NO:2002)  
 25 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1992) (SEQ. ID NO:2003)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1993) (SEQ. ID NO:2004)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1994) (SEQ. ID NO:2005)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1995) (SEQ. ID NO:2006)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1996) (SEQ. ID NO:2007)  
 30 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1997) (SEQ. ID NO:2008)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1998) (SEQ. ID NO:2009)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:1999) (SEQ. ID NO:2010)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2000) (SEQ. ID NO:2011)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2001) (SEQ. ID NO:2012)  
 35 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2002) (SEQ. ID NO:2013)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2003) (SEQ. ID NO:2014)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2004) (SEQ. ID NO:2015)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2005) (SEQ. ID NO:2016)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2006) (SEQ. ID NO:2017)  
 40 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2007) (SEQ. ID NO:2018)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2008) (SEQ. ID NO:2019)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2009) (SEQ. ID NO:2020)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2010) (SEQ. ID NO:2021)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2011) (SEQ. ID NO:2022)  
 45 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2012) (SEQ. ID NO:2023)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2013) (SEQ. ID NO:2024)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2014) (SEQ. ID NO:2025)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2015) (SEQ. ID NO:2026)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2016) (SEQ. ID NO:2027)  
 50 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2017) (SEQ. ID NO:2028)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2018) (SEQ. ID NO:2029)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2019) (SEQ. ID NO:2030)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2020) (SEQ. ID NO:2031)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2021) (SEQ. ID NO:2032)  
 55 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2022) (SEQ. ID NO:2033)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2023) (SEQ. ID NO:2034)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2024) (SEQ. ID NO:2035)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2025) (SEQ. ID NO:2036)  
 5'-GCGBGGCTGTBCCTCGCTGGGCCC-3' (FRAG. NO:2026) (SEQ. ID NO:2037)

- 5'-GTCBTGGCGCGCTCGGGCCGGGC-3' (FRAG. NO:2027) (SEQ. ID NO:2038)  
5'-TCBTGGCGCGCTCGGGCCGGGC-3' (FRAG. NO:2028) (SEQ. ID NO:2039)  
5'-CBTGGCGCGCTCGGGCCGGGC-3' (FRAG. NO:2029) (SEQ. ID NO:2040)  
5'-BTGGCGCGCTCGGGCCGGGC-3' (FRAG. NO:2030) (SEQ. ID NO:2041)  
5 5'-TGGCGCGCTCGGGCCGGGC-3' (FRAG. NO:2031) (SEQ. ID NO:2042)  
5'-GGCGCGCTCGGGCCGGGC-3' (FRAG. NO:2032) (SEQ. ID NO:2043)  
5'-GCGGCGCTCGGGCCGGGC-3' (FRAG. NO:2033) (SEQ. ID NO:2044)  
5'-CGGCGCTCGGGCCGGGC-3' (FRAG. NO:2034) (SEQ. ID NO:2045)  
5'-GGCGTCGGGCGGGC-3' (FRAG. NO:2035) (SEQ. ID NO:2046)  
10 5'-GCGTCGGGCGGGC-3' (FRAG. NO:2036) (SEQ. ID NO:2047)  
5'-CGTCGGGCGGGC-3' (FRAG. NO:2037) (SEQ. ID NO:2048)  
5'-GTCGGGCGGGC-3' (FRAG. NO:2038) (SEQ. ID NO:2049)  
5'-TCGGGCGGGC-3' (FRAG. NO:2039) (SEQ. ID NO:2050)  
5'-CGGGCGGGC-3' (FRAG. NO:2040) (SEQ. ID NO:2051)  
15 5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2041) (SEQ. ID NO:2052)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2042) (SEQ. ID NO:2053)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2043) (SEQ. ID NO:2054)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2044) (SEQ. ID NO:2055)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2045) (SEQ. ID NO:2056)  
20 5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2046) (SEQ. ID NO:2057)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2047) (SEQ. ID NO:2058)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2048) (SEQ. ID NO:2059)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2049) (SEQ. ID NO:2060)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2050) (SEQ. ID NO:2061)  
25 5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2051) (SEQ. ID NO:2062)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2052) (SEQ. ID NO:2063)  
5'-CCGCBGGCCBGGGCGCGCCGCCGGCCGGCCG-3' (FRAG. NO:2053) (SEQ. ID NO:2064)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2054) (SEQ. ID NO:2065)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2055) (SEQ. ID NO:2066)  
30 5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2056) (SEQ. ID NO:2067)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2057) (SEQ. ID NO:2068)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2058) (SEQ. ID NO:2069)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2059) (SEQ. ID NO:2070)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2060) (SEQ. ID NO:2071)  
35 5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2061) (SEQ. ID NO:2072)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2062) (SEQ. ID NO:2073)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2063) (SEQ. ID NO:2074)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2064) (SEQ. ID NO:2075)  
5'-CCGCBGGCCBGGGCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2065) (SEQ. ID NO:2076)  
40 5'-GCBGGCCBGGGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2066) (SEQ. ID NO:2077)  
5'-CBGGCCBGGGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2067) (SEQ. ID NO:2078)  
5'-BGGCCBGGGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2068) (SEQ. ID NO:2079)  
5'-GGCCBGGGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2069) (SEQ. ID NO:2080)  
5'-GCCBGGGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2070) (SEQ. ID NO:2081)  
45 5'-CCBGGGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2071) (SEQ. ID NO:2082)  
5'-CBGGGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2072) (SEQ. ID NO:2083)  
5'-BGGGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2073) (SEQ. ID NO:2084)  
5'-GGGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2074) (SEQ. ID NO:2085)  
5'-GGCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2075) (SEQ. ID NO:2086)  
50 5'-GCGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2076) (SEQ. ID NO:2087)  
5'-CGCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2077) (SEQ. ID NO:2088)  
5'-GCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2078) (SEQ. ID NO:2089)  
5'-CGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2079) (SEQ. ID NO:2090)  
5'-GCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2080) (SEQ. ID NO:2091)  
55 5'-CCGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2081) (SEQ. ID NO:2092)  
5'-CGCCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2082) (SEQ. ID NO:2093)  
5'-GCGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2083) (SEQ. ID NO:2094)  
5'-CCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2084) (SEQ. ID NO:2095)  
5'-CGCGCCGGCCGGCCGGCCG-3' (FRAG. NO:2085) (SEQ. ID NO:2096)  
60 5'-GGCCGGCCGGCCGGCCG-3' (FRAG. NO:2086) (SEQ. ID NO:2097)

69

- 5'-CCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2146) (SEQ. ID NO:2157)  
5'-CGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2147) (SEQ. ID NO:2158)  
5'-GGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2148) (SEQ. ID NO:2159)  
5'-GCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2149) (SEQ. ID NO:2160)  
5'-CTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2150) (SEQ. ID NO:2161)  
5'-TTGCCCGCCCGGCCCGG-3' (FRAG. NO:2151) (SEQ. ID NO:2162)  
5'-TGCCCGCCCGGCCCGG-3' (FRAG. NO:2152) (SEQ. ID NO:2163)  
5'-GCCCGCCCGGCCCGG-3' (FRAG. NO:2153) (SEQ. ID NO:2164)  
5'-CCCGCCCGGCCCGG-3' (FRAG. NO:2154) (SEQ. ID NO:2165)  
5'-CCGCCCGGCCCGG-3' (FRAG. NO:2155) (SEQ. ID NO:2166)  
5'-CGCCCGGCCCGG-3' (FRAG. NO:2156) (SEQ. ID NO:2167)  
5'-GCCCGGCCCGG-3' (FRAG. NO:2157) (SEQ. ID NO:2168)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2158) (SEQ. ID NO:2169)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2159) (SEQ. ID NO:2170)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCCTBGGGCC-3' (FRAG. NO:2160) (SEQ. ID NO:2171)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCCTBGGGC-3' (FRAG. NO:2161) (SEQ. ID NO:2172)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCCTBGGG-3' (FRAG. NO:2162) (SEQ. ID NO:2173)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCCTBGG-3' (FRAG. NO:2163) (SEQ. ID NO:2174)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCCTBG-3' (FRAG. NO:2164) (SEQ. ID NO:2175)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCCTB-3' (FRAG. NO:2165) (SEQ. ID NO:2176)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCCT-3' (FRAG. NO:2166) (SEQ. ID NO:2177)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGCC-3' (FRAG. NO:2167) (SEQ. ID NO:2178)  
5'-GGCGGGGGCGGCGGCGCTGGCTCGC-3' (FRAG. NO:2168) (SEQ. ID NO:2179)  
5'-GGCGGGGGCGGCGGCGCTGGCTCG-3' (FRAG. NO:2169) (SEQ. ID NO:2180)  
5'-GGCGGGGGCGGCGGCGCTGGCTC-3' (FRAG. NO:2170) (SEQ. ID NO:2181)  
5'-GGCGGGGGCGGCGGCGCTGGCT-3' (FRAG. NO:2171) (SEQ. ID NO:2082)  
5'-GGCGGGGGCGGCGGCGCTGGC-3' (FRAG. NO:2172) (SEQ. ID NO:2183)  
5'-GGCGGGGGCGGCGGCGCTGG-3' (FRAG. NO:2173) (SEQ. ID NO:2184)  
5'-GGCGGGGGCGGCGGCGCTG-3' (FRAG. NO:2174) (SEQ. ID NO:2185)  
5'-GGCGGGGGCGGCGGCGCCT-3' (FRAG. NO:2175) (SEQ. ID NO:2186)  
5'-GGCGGGGGCGGCGGCGGCC-3' (FRAG. NO:2176) (SEQ. ID NO:2187)  
5'-GGCGGGGGCGGCGGCGC-3' (FRAG. NO:2177) (SEQ. ID NO:2188)  
5'-GGCGGGGGCGGCGGCG-3' (FRAG. NO:2178) (SEQ. ID NO:2189)  
5'-GGCGGGGGCGGCGGC-3' (FRAG. NO:2179) (SEQ. ID NO:2190)  
5'-GGCGGGGGCGGCGG-3' (FRAG. NO:2180) (SEQ. ID NO:2191)  
5'-GGCGGGGGCGGCG-3' (FRAG. NO:2181) (SEQ. ID NO:2192)  
5'-GGCGGGGGCGGC-3' (FRAG. NO:2182) (SEQ. ID NO:2193)  
5'-GGCGGGGGCGG-3' (FRAG. NO:2183) (SEQ. ID NO:2194)  
5'-GCGGGGGCGGCGGCGCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2184) (SEQ. ID NO:2195)  
5'-CGGGGGCGGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2185) (SEQ. ID NO:2196)  
5'-GGGGGGCGGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2186) (SEQ. ID NO:2197)  
5'-GGGGGGCGGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2187) (SEQ. ID NO:2198)  
5'-GGGGGGCGGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2188) (SEQ. ID NO:2199)  
5'-GGGGGGCGGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2189) (SEQ. ID NO:2200)  
5'-GCGGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2190) (SEQ. ID NO:2201)  
5'-CGGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2191) (SEQ. ID NO:2202)  
5'-GGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2192) (SEQ. ID NO:2203)  
5'-GCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2193) (SEQ. ID NO:2204)  
5'-CGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2194) (SEQ. ID NO:2205)  
5'-GGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2195) (SEQ. ID NO:2206)  
5'-GCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2196) (SEQ. ID NO:2207)  
5'-CGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2197) (SEQ. ID NO:2208)  
5'-GCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2198) (SEQ. ID NO:2209)  
5'-CCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2199) (SEQ. ID NO:2210)  
5'-CTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2200) (SEQ. ID NO:2211)  
5'-TGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2201) (SEQ. ID NO:2212)  
5'-GGCTCGCCTBGGGCCCC-3' (FRAG. NO:2202) (SEQ. ID NO:2213)  
5'-GCTCGCCTBGGGCCCC-3' (FRAG. NO:2203) (SEQ. ID NO:2214)  
5'-CTCGCCTBGGGCCCC-3' (FRAG. NO:2204) (SEQ. ID NO:2215)

- 5'-TCGCCTBGGGCCCC-3' (FRAG. NO:2205) (SEQ. ID NO:2216)  
5'-CGCCTBGGGCCCC-3' (FRAG. NO:2206) (SEQ. ID NO:2217)  
5'-GCCTBGGGCCCC-3' (FRAG. NO:2207) (SEQ. ID NO:2218)  
5'-CCTBGGGCCCC-3' (FRAG. NO:2208) (SEQ. ID NO:2219)  
5 5'-CTBGGGCCCC-3' (FRAG. NO:2209) (SEQ. ID NO:2220)  
5'-GGGTGGGCBGCGCGCC-3' (FRAG. NO:2210) (SEQ. ID NO:2221)  
5'-GGTCGGCGBBBGCTCGTCGTGGC-3' (FRAG. NO:2211) (SEQ. ID NO:2222)  
5'-GGTCGGCGBBBGCTCGTCGTGG-3' (FRAG. NO:2212) (SEQ. ID NO:2223)  
5'-GGTCGGCGBBBGCTCGTCGTG-3' (FRAG. NO:2213) (SEQ. ID NO:2224)  
10 5'-GGTCGGCGBBBGCTCGTCGT-3' (FRAG. NO:2214) (SEQ. ID NO:2225)  
5'-GGTCGGCGBBBGCTCGTCG-3' (FRAG. NO:2215) (SEQ. ID NO:2226)  
5'-GGTCGGCGBBBGCTCGTC-3' (FRAG. NO:2216) (SEQ. ID NO:2227)  
5'-GGTCGGCGBBBGCTCGT-3' (FRAG. NO:2217) (SEQ. ID NO:2228)  
5'-GGTCGGCGBBBGCTCG-3' (FRAG. NO:2218) (SEQ. ID NO:2229)  
15 5'-GGTCGGCGBBBGCTC-3' (FRAG. NO:2219) (SEQ. ID NO:2230)  
5'-GGTCGGCGBBBGCT-3' (FRAG. NO:2220) (SEQ. ID NO:2231)  
5'-GGTCGGCGBBBG-3' (FRAG. NO:2221) (SEQ. ID NO:2232)  
5'-GGTCGGCGBBBG-3' (FRAG. NO:2222) (SEQ. ID NO:2233)  
5'-GGTCGGCGBBB-3' (FRAG. NO:2223) (SEQ. ID NO:2234)  
20 5'-GGTCGGCGBB-3' (FRAG. NO:2224) (SEQ. ID NO:2235)  
5'-GTCGGCGBBBGCTCGTCGTGGC-3' (FRAG. NO:2225) (SEQ. ID NO:2236)  
5'-TCGGCGBBBGCTCGTCGTGGC-3' (FRAG. NO:2226) (SEQ. ID NO:2237)  
5'-CGGCGBBBGCTCGTCGTGGC-3' (FRAG. NO:2227) (SEQ. ID NO:2238)  
5'-GGCBBBGCTCGTCGTGGC-3' (FRAG. NO:2228) (SEQ. ID NO:2239)  
25 5'-GCGBBBGCTCGTCGTGGC-3' (FRAG. NO:2229) (SEQ. ID NO:2240)  
5'-CGBBGCTCGTCGTGGC-3' (FRAG. NO:2230) (SEQ. ID NO:2241)  
5'-GBBGCTCGTCGTGGC-3' (FRAG. NO:2231) (SEQ. ID NO:2242)  
5'-BBBGCTCGTCGTGGC-3' (FRAG. NO:2232) (SEQ. ID NO:2243)  
5'-BGBGCTCGTCGTGGC-3' (FRAG. NO:2233) (SEQ. ID NO:2244)  
30 5'-GBGCTCGTCGTGGC-3' (FRAG. NO:2234) (SEQ. ID NO:2245)  
5'-BGCTCGTCGTGGC-3' (FRAG. NO:2235) (SEQ. ID NO:2246)  
5'-GCTCGTCGTGGC-3' (FRAG. NO:2236) (SEQ. ID NO:2247)  
5'-CTCGTCGTGGC-3' (FRAG. NO:2237) (SEQ. ID NO:2248)  
5'-TCGTCGTGGC-3' (FRAG. NO:2238) (SEQ. ID NO:2249)  
35 5'-GGGGCCCCGCGCGCCCCC-3' (FRAG. NO:2239) (SEQ. ID NO:2250)  
5'-GGGGCCCCGCGCGCCCCC-3' (FRAG. NO:2240) (SEQ. ID NO:2251)  
5'-GGGGCCCCGCGCGCCCCC-3' (FRAG. NO:2241) (SEQ. ID NO:2252)  
5'-GGGGCCCCGCGCGCCCC-3' (FRAG. NO:2242) (SEQ. ID NO:2253)  
5'-GGGGCCCCGCGCGCCC-3' (FRAG. NO:2243) (SEQ. ID NO:2254)  
40 5'-GGGGCCCCGCGCGC-3' (FRAG. NO:2244) (SEQ. ID NO:2255)  
5'-GGGGCCCCGCGC-3' (FRAG. NO:2245) (SEQ. ID NO:2256)  
5'-GGGGCCCCGCG-3' (FRAG. NO:2246) (SEQ. ID NO:2257)  
5'-GGGGCCCCG-3' (FRAG. NO:2247) (SEQ. ID NO:2258)  
5'-GGGGCCCC-3' (FRAG. NO:2248) (SEQ. ID NO:2259)  
45 5'-GGCCCCGCGCGCCCCC-3' (FRAG. NO:2249) (SEQ. ID NO:2260)  
5'-GCCCCGCGCGCCCCC-3' (FRAG. NO:2250) (SEQ. ID NO:2261)  
5'-CCCCGCGCGCCCCC-3' (FRAG. NO:2251) (SEQ. ID NO:2262)  
5'-CCCGCGCGCCCCC-3' (FRAG. NO:2252) (SEQ. ID NO:2263)  
5'-CCGCGCGCCCCC-3' (FRAG. NO:2253) (SEQ. ID NO:2264)  
50 5'-CGCGCGCCCCC-3' (FRAG. NO:2254) (SEQ. ID NO:2265)  
5'-GCGCGCCCCC-3' (FRAG. NO:2255) (SEQ. ID NO:2266)  
5'-CGCGCCCCC-3' (FRAG. NO:2256) (SEQ. ID NO:2267)  
5'-GCCCGCCCCC-3' (FRAG. NO:2257) (SEQ. ID NO:2268)  
5'-GGGGCGCGCGGGCGCGGG-3' (FRAG. NO:2258) (SEQ. ID NO:2269)  
55 5'-GGCGGGBGCGGGCGGGCGGG-3' (FRAG. NO:2259) (SEQ. ID NO:2270)  
5'-GGCGGTCGCGCGCGCGCGCG-3' (FRAG. NO:2260) (SEQ. ID NO:2271)  
5'-GCGCGGCBGCGCGCGCGCG-3' (FRAG. NO:2261) (SEQ. ID NO:2272)  
5'-GCGCBGCGCGCGCGCG-3' (FRAG. NO:2262) (SEQ. ID NO:2273)  
5'-GGGCGGGTGGCTGCCCTGCGCGCG-3' (FRAG. NO:2263) (SEQ. ID NO:2274)

- 5'-GGGCTGCTGCGCGGCGGCTCCGGCGA-3' (FRAG. NO:2264) (SEQ. ID NO:2275)  
 5'-CTCCCGGGCGGGGCGGGCGCGGG-3' (FRAG. NO:2265) (SEQ. ID NO:2276)  
 5'-GGGCTGCGCGGTCCGGGCCCCCTTGTCCGCG-3' (FRAG. NO:2266) (SEQ. ID NO:2277)  
 5'-GCGCTCGCGCCGCTGCCGG-3' (FRAG. NO:2267) (SEQ. ID NO:2278)  
 5'-GCGCCGCTTGGCCTTGTGCGGCG-3' (FRAG. NO:2268) (SEQ. ID NO:2279)  
 5'-GCTGTCTCCBCGCGCTGG-3' (FRAG. NO:2269) (SEQ. ID NO:2280)  
 5'-GCCGGBGGCCGGCCBGGTCCCGCG-3' (FRAG. NO:2270) (SEQ. ID NO:2281)  
 5'-CCCGGCGGCGGCBGGBGGGCGGGCTGGGC-3' (FRAG. NO:2271) (SEQ. ID NO:2282)  
 5'-GTCTCTCCCGCCCCGGCCGCGCG-3' (FRAG. NO:2272) (SEQ. ID NO:2283)  
 5'-GGGCGTCCGCTCCGGGCGCTCGGG-3' (FRAG. NO:2273) (SEQ. ID NO:2284)  
 5'-GCGGGCACGCGGCGGCTCTGGCGTCGGC-3' (FRAG. NO:2274) (SEQ. ID NO:2285)

Where B is adenosine, or, more preferably, replaces adenosine and is a universal base, and adenosine A2a receptor agonist, an adenosine A2b receptor antagonist, an adenosine A3 receptor antagonist, or an adenosine A1 receptor antagonist

### 15 Bradykinin Receptor Anti-sense Oligonucleotide Fragments

- 5'-GGTGBCBTTG BGCBTGTCGG CGCGTCCCG TTBBBGTGG GCCGCCAGC CCAGCCACTC CACTTGGGGG CGGGTGGCCA  
 GCACGAACAG CACCCAGAGG AAGGGGGGCG GCCAGAAGG GCAGCCCGCA GGCCAGGATC AGGTCTGCTG CGGCCGGAGA  
 TAATGGCATT CACCAACGCG CGGCCAGCG CACGCCGCG ATCCGGCCCG GGTCTGACC TGCAGCCCC GTCTCCTTGG  
 CATTCTGGG CCCCAGTCAC TCCTCTCCCT GCCCCCTTG CTGGGGCAGG GACGGGGT BCBTTGBGCB TGTCGGCGCG  
 GTCCGTTBB GBGTGGGCC GCCAGCCAG CCACTCACT TGGGGGCGG TGGCCAGCAC GAACAGCACC CAGAGGAAGG  
 GGGGCGGCC AGAAGGGCAG CCCGAGGCC AGGATCAGGT CTGCTGCGG CGGAGATAAT GGCATTCACC ACGCGGCGGC  
 CCAGCGCAC CGCGCATCC GGCCGGGT CTGACCTGCA GCCCCGTCT CTTGGCATT CTTGGCCCC AGTCACTCCT  
 CTCCTGCCC CCCTTGCTGG GGCAGGGACG GCCGTGTGT CBTGGTGCT GCCGTTTGB GGTBTGGCGC TCCBCCBTT  
 CCCTTTTCTC TTGTTTTC GTTCTCTTG CCGTCTGTGG TT-3' (FRAG. NO:2275) (SEQ. ID NO:2286)  
 5'-GGTGBCBTTGBGCBTGTGCGCGC-3' (FRAG. NO:2276) (SEQ. ID NO:2287)  
 5'-GGTCCCGTTBBBGTGGGCC-3' (FRAG. NO:2277) (SEQ. ID NO:2288)  
 5'-GCCAGCCAGCCACTCCACTTGGGGC-3' (FRAG. NO:2278) (SEQ. ID NO:2289)  
 5'-GGGTGGCCAGCACGAACAGCACCCAGAGGAAGGGGGC-3' (FRAG. NO:2279) (SEQ. ID NO:2290)  
 5'-GGCCAGAAGGGCAGCCCGCAGGCCAGGATCAGGTCTGCTGCGGCC-3' (FRAG. NO:2280) (SEQ. ID NO:2291)  
 5'-GGAGATAATGGCATTACCAACGCGGC-3' (FRAG. NO:2281) (SEQ. ID NO:2292)  
 5'-GGCCAGCGCACGCCGCGCATCCGGCCC-3' (FRAG. NO:2282) (SEQ. ID NO:2293)  
 5'-GGGTCTGACCTGCAGCCCC-3' (FRAG. NO:2283) (SEQ. ID NO:2294)  
 5'-GTCTCCTTGGCATTCTGGGCC-3' (FRAG. NO:2284) (SEQ. ID NO:2295)  
 5'-CAGTCACTCTCTCCCTGCCCC-3' (FRAG. NO:2285) (SEQ. ID NO:2296)  
 5'-CTTGCTGGGGCAGGGACGG-3' (FRAG. NO:2286) (SEQ. ID NO:2297)  
 5'-GGTGBCBTTGBGCBTGTGCGCGC-3' (FRAG. NO:2287) (SEQ. ID NO:2298)  
 5'-GGTCCCGTTBBBGTGGGCC-3' (FRAG. NO:2288) (SEQ. ID NO:2299)  
 5'-GCCAGCCAGCCACTCCACTTGGGGC-3' (FRAG. NO:2289) (SEQ. ID NO:2300)  
 5'-GGGTGGCCAGCACGAACAGCACCCAGAGGAAGGGGGC-3' (FRAG. NO:2290) (SEQ. ID NO:2301)  
 5'-GGCCAGAAGGGCAGCCCGCAGGCCAGGATCAGGTCTGCTGCGGCC-3' (FRAG. NO:2291) (SEQ. ID NO:2302)  
 5'-GGAGATAATGGCATTACCAACGCGGC-3' (FRAG. NO:2292) (SEQ. ID NO:2303)  
 5'-GGCCAGCGCACGCCGCGCATCCGGCCC-3' (FRAG. NO:2293) (SEQ. ID NO:2304)  
 5'-GGGTCTGACCTGCAGCCCC-3' (FRAG. NO:2294) (SEQ. ID NO:2305)  
 5'-GTCTCCTTGGCATTCTGGGCC-3' (FRAG. NO:2295) (SEQ. ID NO:2306)  
 5'-CAGTCACTCTCTCCCTGCCCC-3' (FRAG. NO:2296) (SEQ. ID NO:2307)  
 5'-CTTGCTGGGGCAGGGACGG-3' (FRAG. NO:2297) (SEQ. ID NO:2308)  
 5'-CCGTGTGTGCBGTGGTGTG-3' (FRAG. NO:2298) (SEQ. ID NO:2309)  
 5'-CCCGTTTGBGGBTGTGGC-3' (FRAG. NO:2299) (SEQ. ID NO:2310)  
 5'-GCTCCBCCBTTCCCTTTTCTCC-3' (FRAG. NO:2300) (SEQ. ID NO:2311)  
 5'-TTGTTTCCGTTTCTCTTG-3' (FRAG. NO:2301) (SEQ. ID NO:2312)  
 5'-CCGTCTGTGGTT-3' (FRAG. NO:2302) (SEQ. ID NO:2313)

In one preferred embodiment, the links between neighboring mononucleotides are

phosphodiester links. In another preferred, at least one mononucleotide phosphodiester residue of the anti-sense oligonucleotide(s) is substituted by a methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, 2'-O-methyl, methylene(methyimino), methyleneoxy (methylimino), phosphoramidate residues, and combinations thereof. The MTA oligos having one or more phosphodiester residues substituted by one or more of the other residues are generally longer lasting, given that these residues are more resistant to hydrolysis than the phosphodiester residue. In some cases up to about 10%, about 30%, about 50%, about 75%, and even all phosphodiester residues may be substituted (100%).

Typically, the multiple target anti-sense oligonucleotide (MTA oligo) of the invention comprises at least about 7 mononucleotides, in some instances up to 60 and more mononucleotides, preferably about 10 to about 36, and more preferably about 12 to about 21 mononucleotides. However, other lengths are also suitable depending on the length of the target macromolecule. Examples of the MTA oligos of the invention are provided in Table 3 below, which includes ninety-four sequences (SEQ ID NOS.: 2317 through 2411).

**Table 3: MTA Oligos, Location Targeted & Target**

MTA Oligo								SEQ. ID	Location	Compound	Target	
20									No.	Targeted		
<u>HUMNFKBP65A AS</u>												
25	CCC	GGC	CCC	GCC	TCG	TGC	C	2317	5' = 1	EPI	2192	
	CGT	CCB	TGC	CGC	GGG	CCC		2318	5' = 28 (AUG)	EPI	2193	
	GCC	CCG	CTG	CTT	GGG	CTG	CTC					
	TGC	CGG	G					2319	5' = 65	EPI	2194	
30	TCT	GTG	CTC	CTC	TCG	CCT	GGG	2320	5' = 137	EPI	2195	
	TGG	TGG	GGT	GGG	TCT	TGG	TGG	2321	5' = 159	EPI	2196	
	CTG	TCC	CTG	GTC	CTG	TG		2322	5' = 196	EPI	2197	
	GGT	CCC	GCT	TCT	TC			2323	5' = 362	EPI	2198	
	GGG	GTT	GTT	GTT	GGT	CTG	G	2324	5' = 401	EPI	2199	
	TGT	CCT	CTT	TCT	GC			2325	5' = 656	EPI	2200	

**Table 3: MTA Oligos, Location Targeted & Target (Cont'd)**

	MTA Oligo	No.	SEQ. ID Targeted	Location	Compound	Target
5	GCC TCG GGC CTC CC	2326	5'=697	EPI	2201	
	GGC TGG GGT CTG CGT	2327	5'=769	EPI	2202	
	GGC CGG GGG TCG GTG GGT					
10	GGG CCG CTG	2328	5'=953	EPI	2203	
	GGG CTG GGG TGC TGG CTT GGG G	2329	5'=1022	EPI	2204	
	GGG GCT GGG GCC TGG GCC	2330	5'=1208	EPI	2205	
	GGC TGG GTG GGC TTG GGG GC	2331	5'=1272	EPI	2206	
	GCT GGG TCT GTG CTG TTG CC	2332	5'=1362	EPI	2207	
	GTT GTG TGG GGG GCC	2333	5'=1451	EPI	2208	
15	GCT GGG TCG GGG GGC CTC TGG					
	GCT GTC	2334	5'=1511	EPI	2209	
	GCC CCG GGG CCC CC	2335	5'=1550	EPI	2210	
	TGG CTC CCC CCT CC	2336	5'=1772	EPI	2211	
	GCT CCC CCC TTT CC	2337	5'=1863	EPI	2212	
20	CGG ACG AAG ACA GAG A	2338	5'=1979	EPI	2213	
	GGC TTT GTG GGC TC	2339	5'=2011	EPI	2214	
	GCC TGC TCT CCC CC	2340	5'=2312	EPI	2215	
	CCC GGC CCC GCC BCG BBC C	2341	intron	EPI	2192-01A	HSU50136 C4 Synthase
25	CCC GGC CCC GCC BCG BBC C	2342	intron	EPI	2192-01B	
	CCC GGC CCC GCC BCG BBC C	2343	5'untr	EPI	2192-02A	HUMLIPOX 5-LO
	CCC GGC CCC GCC BCG	2344	5'untr	EPI	2192-02B	
	CCC GBC CCC GCC TCB BG	2345	trans	EPI	2192-03A	HSNFKBS
30	subunit CCC GBC CCC GCC TC	2346	trans	EPI	2192-03B	
	CCG GCC CCG CCT C	2347	5'untr	EPI	2192-04	TGFBR1
	CCC GBB CCC GCB TBG TGC C	2348	5'trans	EPI	2192-05A	HSU58198 II enhan
35	CCC GCB TBG TGC C	2349	5'untr	EPI	2192-05B	
	CCC GGB CCC BCC BBG TGC C	2350	3'trans	EPI	2192-06	HSVECAD
	CBG BBC CCG CCT CGT GCC	2351	intron	EPI	2192-07A	NFKB2
	C CCG CCT CGT GCC	2352	intron	EPI	2192-07B	NFKB2
	CCG GCB CCG CCT CBT GCC	2353	5'trans	EPI	2192-08	Carboxypep
	CCG GCC CCG CCB CBT GCC	2354	3'trans	EPI	2192-09	HUMADRA2C
40	CCC GBC CCC GBC TCG	2355	5'untrs	EPI	2192-10	α2adr kidney
	CCC GGC CBC GBC TCG	2356	5'untrs	EPI	2192-11	HUMFK506B
	CCC GGC CCB GCC TBG	2357	5'UTR	EPI	2192-12	HSNBARKS1
45	(NFKB1)					Badr kinase
	CCC GGC BCB GBC TCG TBC C	2358	3'UTR	EPI	2192-13	HSNFXN1
	(transcrp.)					HSILF
50	CCC GGC CCC GCC BCG	2359		EPI-2192-14		Factor ILF)
	Syn/5-LO					NFKB/C4
	MTA					/TGFBrecl
	CCC GGC CCC GCC BCG	2360		EPI-2192-15		NFKB/C4 Syn
55	TCC BTG CCG CGG GC	2361	3' trans	EPI-2193-01		/5-LO MTA
	TCC BTG CCB CGG GCC	2362	3' trans	EPI-2193-02		MET Oncogene
	TCC BTG CCB CGG GCC	2363	mid cod	EPI-2193-03		HSFGR2 (IG)
	TCC BTG CCB CGG GCC	2364	mid cod	EPI-2193-04		5-LO
	GTC CBT GBC GCG G	2365	3'trans	EPI-2193-05		HUMTK14
	TC CBT GBC GCG GG	2366	AUG			HUMTNFR
60					Probl.HUMPTCH	cardiac
	K+channel					
	TCT GBC CTC CTC TBB CCT GGG	2367	intr	EPI-2195-01		HUMCSPA
65	cytotox.					
	CTG TGC BCC TBB CBC CTG GG	2368	intr	EPI-2195-02		ser. protease
	TGT GBT CCB CTB GBC TGG G	2369		EPI-2195-03		HSINOSX08
70						inducible NOS
	TCT GTB CTC BBC TCB CCT G	2370		EPI-2195-04		HUMACHRM2
75	TGC TCC TCB CBB CTG GG	2371		EPI-2195-05		musc.
						m2 acetylch.
						rec.
						s86371sl
						Neurokinin 3
						rec
						HUMIPIA macro



**Table 3:** MTA Oligos, Location Targeted & Target (Cont'd)

MTA Oligo	No.	SEQ. ID Targeted	Location	Compound	Target
					inflam. factor
CTC CTC TBG CCT GG	2372			EPI-2195-06	HSNBARKS4
GTG CTC CBB TCB BCT GGG	2373			EPI-2195-07	β-adr rec kinase
GTG CBC CBB TCB CCT GGG	2374			EPI-2195-08	HSTNFR2SO6
					TNF R2
					humfkbp
					fk506
TCT GTG CBC CTC TBG BCT	2375	exon		EPI-2195-09	binding protein
					HSNBARKS1 β-adr.
					receptor
CTG TBB TCC TBB CBC CTG G	2376	intron		EPI-2195-10	kinase
TGT GCT BBT CBC BCB TGG G	2377			EPI-2195-11	HUMIL8
					HSU50157
					PDE4
GTG CBC CBC TCB CCT G	2378	intron/exon		EPI-2195-12	IL-2 R
CTG TGC BCC TCT C	2379	3'UTR		EPI-2203-05	IL-6 R
					HSIL6R
CBG TGC BCC BCT CBC CTG	2380	intr/ex		EPI-2203-06A	HSIL2rG6
G TGC BCC BCT CBC CTG	2381	intr/ex		EPI-2203-06B	HSIL2rG6
CBC CTC TCB CCT GGG	2382	coding		EPI-2203-07A	HUMIL71
C CTC TCB CCT GGG	2383	coding		EPI-2203-07B	IL-7 HUMIL71
GCT CCB CTC GCC T	2384	coding		EPI-2203-08	IL-6 R
					HSI6REC
TGC TCC TCB CGC C	2385	intron	PDGF A	EPI-2303-09	chain
					HUMPDGFAB
GTT GTT GBT CTG G	2386	3'utr		EPI-2199-01	GATA-4
transcrip.					Factor for
					IL-5
GGT TGB BBT TGG TCT TGG	2387	Coding		EPI-2199-02	TNFr HUMINFA
GGT TGT TGB TGB TCT G	2388	Far 5'UTR		EPI-2199-03	HSSUBP1G
					(Sub P r)
GGG TTB BBG TTG BTC TGG	2389	Coding		EPI-2199-04	Neutrophil
					adh.
					R HUMNARIA
GGG TTB BBG TTG BTC TGG	2390	HSHM2		EPI-2199-05	m2
					muscarinic
					R
TTG TTG TBG BTC TGG	2391	HUML1CAM		EPI-2199-06	L1 leuk.
					adh.
					prot.
GGG TBG BBG BGT CCG CTG	2392	coding		EPI-2203-01	HUMGATA2A
GGG TCB GBG GBT CBG CTG	2393	S71424S2		EPI-2203-02	IGE eps
GGG TBG GTG GGT C	2394	coding		EPI-2203-03	HSGCSFR2
GGG TCG GBG GGT CBG C	2395	HUMITGF		EPI-2203-04	TGFβ3
CCT GGG TGG GCT T		HUMNK65PRO		EPI-2206-01	NFKB/NK & T
					Cell
					Activating
					Protein
GGG TGG GCT TGG G	2396	HUMPEREEB		EPI 2206-02	NFKB/
					Prostagl.
					EP3 Receptor

**Table 3: MTA Oligos, Location Targeted & Target (Cont'd)**

MTA Oligo	No.	SEQ. ID Targeted	Location	Compound	Target
5 CCTGGGTGGGBBTGGG	2397		EPI 2206-03	HSNF2B/GCSF	NFKB/ Granulocyte CSF/Transcr.
10 CCTGGBTGGGCBTGGG	2398		EPI-2206-04	Factor NF2B	HUMLAP/NFKB Leuk. Adhes. Prot.
15 GCCTGBGTGBBCTTGGG	2399		EPI 2206-05	NFKB/ Endotheline	N2 S63833
CCCAGVCCVCCAGGC	2400		EPI 2206-06	NFKBAS13/B	Lymph. Ser Thr Prot. Kinase
20 AGCCCACCCAGGC	2401		EPI 2206-07	NFKBAS13/GCSF1	HSGCSFR1 Rec.
BCCTGGGTGGGCTB	2402		EPI 2206-08	NFKBAS13/GCSF1	/NK7TCELLACT. Prot.
25 GGTGGGCTTGGG	2403		EPI 2206-09	NFKBAS13	/HSTGFB1 TGFB
CCBBGGTGGGCTTGGG	2404		EPI 2206-10	NFKBAS13	/HSTGFB1 TGFB1
30 CTGGGTGGGBBTGGG	2405		EPI 2206-11	NFKBAS13/ HSGCSFR1	
CCBGGGTGGGCTTGG	2406		EPI 2206-12	GCSFR1 NFKBAS13/ HUMCD30A	Lymph. Act. Antig. (Coding)
35 GGGTGGGCTTGG	2407		EPI-2206-12B	NFKBAS13/	
HUMCD30A CCTGBGTGBGCBTGGG	2408		EPI 2206-13	NFKBAS13/ HUMCAMIV	Vasc. Endoth. Cell Adh. Molec.
40					
45 B: Universal Base					

The MTA oligos of Table 3 are suitable for use with two or more of the targets listed in Table 4 below.

**Table 4: Targets for the MTA Oligos of Table 3**

Compound	Target
EPI 2010	Adenosine A1 receptor
EPI 2045	Adenosine A3 receptor
EPI 2873, EPI 2193	NFκB
EPI 1873	Interleukin-1
EPI 1857	Interleukin -5
EPI 2945	Interleukin -4
EPI 2977	Interleukin -8
EPI 2031	5-Lipoxygenase
EPI 1898	Leukotriene C-4 Synthase
EPI 1856	Eotaxin
EPI 1131	ICAM
EPI 1085	VCAM
EPI 2085	TNFα
EPI 1908	PAF
EPI 1925	IL-4 receptor
EPI 2643	β2 adrenergic receptor kinase
EPI 2934	Tryptase
EPI 2033	Major Basic Protein
EPI 2795	Eosinophil Peroxidase

NFκB: nuclear factor κB

ICAM: intracellular adhesion molecule

VCAM: vascular cell adhesion molecule

TNF: tumor necrosis factor

PAF: platelet activating factor

In a most preferred embodiment for use in the lung, the MTA oligo of this invention comprises a desadenosine oligonucleotide, whether an anti-sense to a naturally occurring desthymidine sequence, or by substitution with one or more universal bases in accordance with the invention. The methods for substituting nucleotide, as well as for synthesizing oligonucleotides of a specific sequence, and which bases to employ as universal bases are known in the art, and need not be further provided here, since they are within the knowledge of an artisan.

In a further embodiment of the agent of the invention, the MTA oligo is operatively linked to an agent or molecule which, itself, is internalized or up-taken by living cells. In this manner, the uptake of the agent of the invention is enhanced as is known in the art. Examples of agents or molecules suitable for use with the MTA oligos of this invention are transferrin, asialoglycoprotein, and streptavidin. Others, however, are also suitable.

The present agents are also provided as a pharmaceutical composition comprising an anti-sense oligonucleotide as given above in an amount effective to reduce expression of a target mRNA, by passing through a cell membrane and binding specifically with target mRNA in the cell so as to prevent its translation are another aspect of the present invention. Such compositions are provided in a suitable pharmaceutically acceptable carrier, e.g. sterile pyrogen-free saline solution. The agent of the invention may be formulated with a hydrophobic carrier capable of passing through a cell membrane, e.g. in a liposome, with the liposomes

carried in a pharmaceutically acceptable aqueous carrier. The oligonucleotides may be coupled to an agent which inactivates mRNA, such as a ribozyme. Such oligonucleotides may be administered to a subject in need of such treatment to inhibit the activation of specific receptors, enzymes and/or proteins and/or factors, among other expression products. The pharmaceutical formulation may also comprise chimeric molecules comprising anti-sense oligonucleotides attached to molecules which are known to be internalized by cells. These oligonucleotide conjugates utilize cellular up-take pathways to increase intracellular concentrations of the oligonucleotide. Examples of molecules used in this manner are macromolecules including transferrin, asialoglycoprotein (bound to oligonucleotides via polylysine) and streptavidin, among others.

The anti-sense compound may be contained in the pharmaceutical formulation within a lipid particle or vesicle, such as a liposome or microcrystal. The particles may be of any suitable structure, such as unilamellar or plurilamellar. The one preferred embodiment, the anti-sense oligonucleotide is comprised within the liposome. Positively charged lipids such as N-[1-(2, 3 -dioleoyloxy) propyl] -N, N, N-trimethylammoniumethylsulfate, or "DOTAP," are particularly preferred for such particles and vesicles. However, others are also suitable. The preparation of such lipid particles is well known. See, e.g., US Patent Nos. 4,880,635 to Janoff et al., 4,906,477 to Kurono et al., 4,911,928 to Wallach, 4,917,951 to Wallach, 4,920,016 to Allen et al., 4,921,757 to Wheatley et al., the relevant sections of all of which are herein incorporated in their entireties by reference.

The composition of the invention may be administered by any means which transports the agent to the lungs. The present agents may be administered to the lungs of a patient by any suitable means, but are preferably administered through the respiratory system as a respirable formulation, more preferably in the form of an aerosol comprising respirable particles which, in turn, comprise the agent for respiration or inhalation by the subject. The respirable particles may be in gaseous, liquid or solid form, and they may, optionally, contain other therapeutic ingredients and formulation components.

The particles of the present invention are preferably particles of respirable size, preferably of a size sufficiently small to pass, upon inhalation, through the mouth and larynx and into the bronchi and alveoli of the lungs. In general, particles ranging from about 0.5 to 10 microns in diameter are respirable. However, other sizes may also be suitable. Particles of non-respirable size, of considerably larger diameter, which are included in the respirable formulation tend to deposit in the throat and may be swallowed. Accordingly, it is desirable to minimize the quantity of non-respirable particles in the aerosol. For nasal administration, a particle size in the range of 10-500  $\mu\text{m}$  is preferred to ensure their retention in the nasal cavity.

Liquid pharmaceutical compositions of the agent of the invention for producing a respirable formulation, e.g. an aerosol may be prepared by combining the anti-sense oligo with a suitable vehicle or carrier, such as sterile pyrogen-free water and/or other known pharmaceutically or veterinarily acceptable carrier. Other therapeutic compounds may be included as well as other formulation ingredients as is known in the art.

Solid particulate compositions comprising respirable dry particles of, e.g. the micronized agent of the invention may be prepared by grinding the dry anti-sense compound with a mortar and pestle, and then passing the thus ground, e.g. micronized composition through a screen, e.g. 400 mesh screen, to break up or separate large agglomerates of particles. A solid particulate composition comprising the anti-sense compound may optionally also comprise a dispersant and other known agents, which serve to facilitate the formation of a mist or aerosol. A suitable dispersant is lactose, which may be blended with the anti-sense compound in any suitable ratio, about 1:1 w/w. Other ratios may be utilized as well, and other therapeutic and formulation agents may also be included.

Aerosols of liquid particles comprising the agent may be produced by any suitable means, such as with an insufflator or nebulizer. See, e.g., US Patent No. 4,501,729. Nebulizers are commercially available devices which transform solutions or suspensions of an agent into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, e.g. through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in insufflators and nebulizers comprise the present agent, the agent of this invention, in an amount of about 0.01 to about 40%, preferably less than 20% w/w in a liquid carrier which is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Other carriers are also suitable. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and surfactants, among others.

The pharmaceutical compositions provided herein comprise nucleic acid(s) comprising the anti-sense oligonucleotide(s) described above and one or more surfactants. Suitable surfactants or surfactant components for enhancing the uptake of the anti-sense oligonucleotides of the invention include synthetic and natural as well as full and truncated forms of surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant Protein E, di-saturated phosphatidylcholine (other than dipalmitoyl), dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine; phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholine, dehydroepiandrosterone, dolichols, sulfatidic acid,

glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate; as well as natural and artificial lamellar bodies which are the natural carrier vehicles for the components of surfactant, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitinic acid, non-ionic block copolymers of ethylene or propylene oxides, polyoxypropylene, monomeric and polymeric, polyoxyethylene, monomeric and polymeric, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100 and synthetic surfactants ALEC, Exosurf, Survan and Atovaquone, among others. These surfactants may be used either as single or part of a multiple component surfactant in a formulation, or as covalently bound additions to the 5' and/or 3' ends of the anti-sense oligonucleotides (oligos).

The composition of the invention may be administered by any means which transports the anti-sense nucleotide and the surfactant composition to the lung. The anti-sense compounds disclosed herein may be administered to the lungs of a patient by any suitable means, but are preferably administered by inhalation of an aerosol comprised of respirable particles which comprise the anti-sense compound. The respirable particles may be liquid or solid, and they may optionally contain other therapeutic or diagnostic ingredients as well as other typical ingredients for a particular formulation. Examples of other agents are analgesics such as acetaminophen, anilerdine, aspirin, buprenorphine, butabital, butorphanol, Choline Salicylate, Codeine, Dezocine, Diclofenac, Diflunisal, Dihydrocodeine, Elcatonin, Etodolac, Fenoprofen, Hydrocodone, Hydromorphone, Ibuprofen, Ketoprofen, Ketorolac, Levorphanol, Magnesium Salicylate, Meclofenamate, Mefenamic Acid, Meperidine, Methadone, Methotrimeprazine, Morphine, Nalbuphine, Naproxen, Opium, Oxycodone, Oxymorphone, Pentazocine, Phenobarbital, Propoxyphene, Salsalate, Sodium Salicylate, Tramadol and Narcotic analgesics in addition to those listed above. See, Mosby's Physician's GenRx. Anti-anxiety agents are also useful including Alprazolam, Bromazepam, Buspirone, Chlordiazepoxide, Chlormezanone, Clorazepate, Diazepam, Halazepam, Hydroxyzine, Ketazolam, Lorazepam, Meprobamate, Oxazepam and Prazepam, among others. Anti-anxiety agents associated with mental depression, such as Chlordiazepoxide, Amitriptyline, Loxapine, Maprotiline and Perphenazine, among others. Anti-inflammatory agents such as non-rheumatic Aspirin, Choline Salicylate, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Fluctafenine, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Magnesium Salicylate, Meclofenamate, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Phenylbutazone, Piroxicam, Salsalate, Sodium Salicylate, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolmetin, anti-inflammatories for ocular treatment such as Diclofenac, Flurbiprofen, Indomethacin, Ketorolac, Rimexolone (generally for post-operative treatment), anti-inflammatories for, non-infectious nasal

applications such as Beclomethaxone, Budesonide, Dexamethasone, Flunisolide, Triamcinolone, and the like. Soporifics (anti-insomnia/sleep inducing agents) such as those utilized for treatment of insomnia, including Alprazolam, Bromazepam, Diazepam, Diphenhydramine, Doxylamine, Estazolam, Flurazepam, Halazepam, Ketazolam, Lorazepam, Nitrazepam, Prazepam, Quazepam, Temazepam, Triazolam, Zolpidem and Sopiclone, among others. Sedatives including Diphenhydramine, Hydroxyzine, Methotrimeprazine, Promethazine, Propofol, Melatonin, Trimeprazine, and the like. Sedatives and agents used for treatment of petit mal and tremors, among other conditions, such as Amitriptyline HCl; Chlordiazepoxide, Amobarbital; Secobarbital, Aprobital, Butabarbital, Ethchlorvynol, Glutethimide, L-Tryptophan, Mephobarbital, Methohexital Na, Midazolam HCl, Oxazepam, Pentobarbital Na, Phenobarbital, Secobarbital Na, Thiamylal Na, and many others. Agents used in the treatment of head trauma (Brain Injury/Ischemia), such as Enadoline HCl (e.g. for treatment of severe head injury; orphan status, Warner Lambert), cytoprotective agents, and agents for the treatment of menopause, menopausal symptoms (treatment), e.g. Ergotamine, Belladonna Alkaloids and Phenobarbital, for the treatment of menopausal vasomotor symptoms, e.g. Clonidine, Conjugated Estrogens and Medroxyprogesterone, Estradiol, Estradiol Cypionate, Estradiol Valerate, Estrogens, conjugated Estrogens, esterified Estrone, Estropipate, and Ethinyl Estradiol. Examples of agents for treatment of pre menstrual syndrome (PMS) are Progesterone, Progestin, Gonadotrophic Releasing Hormone, Oral contraceptives, Danazol, Luprolide Acetate, Vitamin B6. Examples of agents for treatment of emotional/psychiatric treatments such as Tricyclic Antidepressants, including Amitriptyline HCl (Elavil), Amitriptyline HCl, Perphenazine (Triavil) and Doxepin HCl (Sinequan). Examples of tranquilizers, antidepressants and anti-anxiety agents are Diazepam (Valium), Lorazepam (Ativan), Alprazolam (Xanax), SSRI's (selective Serotonin reuptake inhibitors), Fluoxetine HCl (Prozac), Sertaline HCl (Zoloft), Paroxetine HCl (Paxil), Fluvoxamine Maleate (Luvox), Venlafaxine HCl (Effexor), Serotonin, Serotonin Agonists (Fenfluramine), and other over the counter (OTC) medications.

The composition of the present invention may be administered into the respiratory system as a formulation including particles of respirable size, e.g. particles of a size sufficiently small to pass through the nose, mouth and larynx upon inhalation and through the bronchi and alveoli of the lungs. In general, respirable particles range from about 0.5 to 10 microns in size. Particles of non-respirable size which are included in the aerosol tend to deposit in the throat and be swallowed, and the quantity of non-respirable particles in the aerosol is thus minimized. For nasal administration, a particle size in the range of 10-500  $\mu\text{m}$  is preferred to ensure retention in the nasal cavity.

Aerosols or mists of solid particles comprising the agent of the invention may likewise be produced with any device that generates solid particulate medicament aerosols or mists. Aerosol and mist generators are suitable for administering solid particulate medicaments. These devices produce respirable particles, as explained above., and generate a volume of aerosol or mist containing a predetermined metered dose of a medicament at a rate suitable for human or animal administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder, e.g. a metered dose of the agent effective to carry out the treatments described herein, is contained in a capsule or a cartridge. These capsules or cartridges are typically made of gelatin or plastic, and may be pierced or opened in situ, and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator may consist either solely of the agent or of a powder blend comprising the agent, a suitable powder diluent, such as lactose, and an optional surfactant as well as other agents. The agent typically comprises from 0.01 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically comprising a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically about 10 to 150  $\mu$ l, although other volumes are also suitable, to produce a fine particle spray containing the active ingredient. Suitable propellants include solvents such as certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and/or mixtures thereof. The formulation may additionally comprise one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents. The aerosol, whether formed from solid or liquid particles, may be produced by the aerosol generator at a rate of from about 10 to 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament may be administered more rapidly.

As already indicated, the agent of this invention is also provided as a composition, comprising the agent of the invention, and a carrier. The carrier is preferably a biologically acceptable carrier, and more preferably a pharmaceutically or veterinarily acceptable carrier in the form of a gaseous, liquid, solid carriers, and mixtures thereof, which are suitable for the different routes of administration intended. The composition may optionally comprise other agents such as other therapeutic compounds known in the art for the treatment of the condition or disease, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents,



dispersants, surfactants, RNA inactivating agents, antioxidants, flavoring agents, propellants and preservatives, as well as other agents known to be utilized in therapeutic compositions. An example of the mRNA inactivating agent is an enzyme, such as ribozyme.

5 The composition generally contains the anti-sense oligonucleotide in an amount of about 0.01 to about 99.99 w/w, preferably about 1 to about 40 w/w, and more preferably about 5 to about 20 w/w of the composition. However, other ingredients, and other amounts of the agent are also suitable within the confines of this invention.

10 The agent of the invention is also provided in various formulations which are tailored for different methods of administration and routes of delivery. The formulations that are contemplated are, for example, a transdermal formulation also containing carrier(s) and other agents suitable for delivery through the skin, mouth, nose, vagina, anus, eyes, ears, other body cavities, intradermally, as a sustained release formulation, intracranial, intrathecally, intravascularly, by inhalation, intrapulmonarily, into an organ, by implantation, including suppositories, cremes, gels, and the like, as is known in the art. In one particular formulation, 15 the agent is suspended or dissolved in a solvent. In another the carrier comprises a hydrophobic carrier, such as lipid particles or vesicles, including liposomes and micro crystals. The preparation of all of these formulations, as well as the ingredients to be utilized are known in the art, and need not be further described here. In one particularly preferred embodiment of the vesicle formulation, the vesicles comprise liposomes containing the anti-sense 20 oligonucleotide. The lipid vesicles may comprise N-(1-[ 2, 3-dioleoxyloxi] propyl) -N,N,N-trimethyl- ammonium methylsulfate as well as other lipids known in the art to provide suitable delivery of DNA to target cells. In one embodiment, the formulation comprises a respirable formulation, such as an aerosol. The agent, composition, and formulation of the invention are provided in bulk, and in unit form, as well as in the form of an implant, a solution or 25 suspension, a capsule or cartridge, which may be openable or piercable as is known in the art.

A kit is also provided, which comprises a delivery device, and in separate containers, the agent, composition or formulation of the invention, and optionally other agents, and instructions for the use of the kit components. In one preferred embodiment, the delivery device comprises a nebulizer which delivers single or multiple metered doses of the 30 formulation. The single metered dose nebulizer may be provided as a disposable kit which is sterilely preloaded with enough agent for one application. The nebulizer may be provided as an insufflator, and the composition in a piercable or openable capsule or cartridge. In a different embodiment, the delivery device comprises a pressurized inhaler, and the agent is in the form of a suspension or solution. The kit may optionally also comprise in a separate 35 container an agent selected from the group consisting of other therapeutic compounds, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants,

surfactants, cell internalized or up taken agents, RNA inactivating agents, antioxidants, flavoring agents, propellants and preservatives, among other suitable additives for the different formulations. When a solvent for the agent or the other ingredients is added, organic solvents and organic solvents mixed with one or more co-solvents may be utilized as well as aqueous solvents as is known in the art.

The agent of the invention may be provided in conjunction with a vector for delivery purposes, or for manufacturing copies thereof. The agent may be operatively linked to the vector as is known in the art. The agent may also be provided within a host cell for amplification of the MTA oligo, and for storage purposes.

The agent of this invention may be utilized by itself or in the form of a composition or various formulations in the treatment of a disease or condition associated with the mRNA corresponding to at least one target gene(s), to genomic flanking regions, initiation codon, intron-exon borders and the like, or the entire sequence of precursor RNAs, including non-coding RNA segments, the 5'-end and the 3'-end, e.g. poly-A segment and oligos targeted to the juxta-section between coding and non-coding regions, and RNA regions encoding proteins, by administration to a subject afflicted with the disease or condition of an amount of the anti-sense oligonucleotide effective to reduce the production or availability, or to increase the degradation by the subject of at least one of the target mRNAs. Typically, the agent is administered in an amount effective to reduce the production or availability, or to increase the degradation of at least two of the target mRNAs. Optionally, the agent is administered directly to the lung (s) of the subject, preferably as a respirable aerosol. Although an artisan will know how to titrate the amount of agent to be administered by the weight of the subjected being treated in accordance with the teachings of this patent, the agent is preferably administered in an amount effective to attain an intracellular concentration of about 0.05 to about 10  $\mu$ M multiple targeted anti-sense oligonucleotide, preferably in an amount effective to attain an intracellular concentration of up to about 5  $\mu$ M multiple targeted anti-sense oligonucleotide.

The treatment provided in this patent is suitable for treating numerous diseases and conditions, and its application is solely limited by the availability of target molecules and their sequences. One type of disease or condition for which this technology is particularly well suited are lung diseases or conditions. For this type of application, at least one of the target mRNA encodes a protein such as the adenosine  $A_1$  receptor, adenosine  $A_2B$  receptor, adenosine  $A_3$  receptor, and bradykinin B2 receptor. However, other targets are also suitable. In one application, the disease or condition is associated with obstruction of the subject's airways, in another specifically with asthma, etc. One of the preferred target proteins comprises the  $Nf\kappa B$  transcription factor, although others which were described above are also suitable. In another preferred application, the disease or condition is associated with inflammation. For this type

of application at least one of the target mRNA preferably encodes a protein selected from the group consisting of interleukins, chemokines, Rantes and receptors thereof. Still another application is for treating a disease or condition associated with an allergy. For this application, the mRNA preferably encodes a target selected from the group consisting of an antibody and an antibody receptor. For the application of this technology to a disease or condition associated with a malignancy or cancer, the mRNA preferably encodes a target selected from the group consisting of oncogenes, an immunoglobulin and an antibody receptor.

Depending on the target organ or tissue, the agent of the invention may be delivered in one of many ways, for example, by a transdermal or systemic route, and more specifically orally, intracavitarily, intranasally, intraanally, intravaginally, transdermally, intrabucally, intravenously, subcutaneously, intramuscularly, intratumorously, into a gland, by implantation, intradermally, and many other routes of administration. The formulation may be, in addition, an implant, slow release, transdermal release, sustained release, and coated with one or more macromolecules to avoid destruction of the agent prior to reaching the selected target. The subject that may be treated by the present agent are varied, and include humans and other animals in general, and in particular vertebrates, and amongst these mammals, and more specifically humans, and small and large, wild and domesticated, marine and farm animals, and preferably humans and domesticated and farm animals. In one aspect of the invention, at least one of the target mRNAs and the subject are of the same species, and in a preferred case they are of human origin. However, since in one embodiment mismatched nucleotides are replaced, mismatched species may also be utilized.

The multiple targeted anti-sense oligonucleotide of this invention may be administered in a broad dose range. Preferable is an amount of about 0.005 to about 150 mg/kg body weight per administration, and the agent may be administered from once in an acute treatment to several doses per day, to a continuous administration to maintain the level of a specific molecule. Preferred doses are about 0.01 to about 75 mg/kg body weight, more preferably about 1 to 50 mg/kg body weight. The method may be administered as a prophylactic or therapeutic method.

The agent of the invention may be produced by selecting two or more targets selected from the group consisting of genes, genomic flanking regions, mRNAs and proteins known to be associated with at least one disease or condition; obtaining RNAs selected from the group consisting of RNAs corresponding to the genes, to genomic flanking regions, initiation codon, intron-exon borders and the like, or the entire sequence of RNAs, including non-coding RNA segments, the 5'-end and the 3'-end, e.g. the poly-A segment and oligos targeted to the juxtaposition between coding and non-coding regions, and RNA segments encoding the target proteins; selecting a segment of a first RNA which is at least about 60% homologous to a

segment of at least a segment of a second RNA; and synthesizing one or more anti-sense oligonucleotide(s) to the one or more RNA segments. In one preferred embodiment, the method further comprises substituting a universal base for at least one, and in some instances all, non-homologous nucleotide in the anti-sense oligonucleotide, and in another preferred  
5 embodiment the method further comprises substituting a methylated cytosine for cytosine in at least one CpG dinucleotide present in the anti-sense oligonucleotide. The technology involved in methylation is known in the art and need not be further described here.

Although the specific length of the MTA oligo is determined by the target's length, and its segments containing few thymidines, the anti-sense oligonucleotide(s) are preferably greater  
10 than about 7 nucleotides long, and up to about 60 nucleotides long, and longer. The specific backbone chemistry may be selected by an artisan based on the teachings provided here and the knowledge of the art at large. One factor that impinges on the selection of the nucleotide bridging residues is the level of nuclease resistance desired and other factors specific to one or the other method of administration. Another factor is the need for localization of the  
15 treatment, to minimize or fully avoid side effects which might otherwise be caused along with the therapeutic effect of the agent.

The following examples are provided to illustrate the present invention, and should not be construed as limiting thereon. In these examples,  $\mu$ M means micromolar, ml means milliliters,  $\mu$ M means micrometers, mm means millimeters, cm means centimeters,  $^{\circ}$ C means  
20 degrees Celsius,  $\mu$ g means micrograms, mg means milligrams, g means grams, kg means kilograms, M means molar, and h means hours.

## **EXAMPLES**

### **Example 1: Design and Synthesis of Anti-sense Oligonucleotides**

The design of anti-sense oligonucleotides against the  $A_1$  and  $A_3$  adenosine receptors may  
25 require the solution of the complex secondary structure of the target  $A_1$  receptor mRNA and the target  $A_3$  receptor mRNA. After generating this structure, anti-sense nucleotide are designed which target regions of mRNA which might be construed to confer functional activity or stability to the mRNA and which optimally may overlap the initiation codon. Other target sites are readily usable. As a demonstration of specificity of the anti-sense effect, other  
30 oligonucleotides not totally complementary to the target mRNA, but containing identical nucleotide compositions on a w/w basis, are included as controls in anti-sense experiments.

The mRNA secondary structure of the adenosine  $A_1$  receptor was analyzed and used as described above. to design a phosphorothioate anti-sense oligonucleotide. The anti-sense oligonucleotide which was synthesized was designated HAd $A_1$ AS and had the following  
35 sequence:

5' -GAT GGA GGG CGG CAT GGC GGG-3' (SEQ ID NO:1)

As a control, a mismatched phosphorothioate anti-sense nucleotide designated HAdAlMM1 was synthesized with the following sequence:

5' -GTA GCA GGC GGG GAT GGG GGC-3' (SEQ ID NO:2)

5 Each oligonucleotide had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligonucleotide was specific for the human and rabbit adenosine A<sub>1</sub> receptor genes, and that the mismatched control was not a candidate for hybridization with any known gene sequence.

10 The secondary structure of the adenosine A<sub>3</sub> receptor mRNA was similarly analyzed and used as described above to design two phosphorothioate anti-sense oligonucleotides. The first anti-sense oligonucleotide (HAdA3AS1) synthesized had the following sequence:

5' -GTT GTT GGG CAT CTT GCC-3' (SEQ ID NO:3)

15 As a control, a mismatched phosphorothioate anti-sense oligonucleotide (HAdA3MM1) was synthesized, having the following sequence:

5' -GTA CTT GCG GAT CTA GGC-3' (SEQ ID NO:4)

A second phosphorothioate anti-sense oligonucleotide (HAdA3AS2) was also designed and synthesized, having the following sequence:

5' -GTG GGC CTA GCT CTC GCC-3' (SEQ ID NO:5)

20 Its control oligonucleotide (HAdA3MM2) had the sequence:

5' -GTC GGG GTA CCT GTC GGC-3' (SEQ ID NO:6)

Phosphorothioate oligonucleotides were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, MD).

25 **Example 2: In Vivo Testing of Adenosine A<sub>1</sub> Receptor Anti-sense Oligos**

30 The anti-sense oligonucleotide against the human A<sub>1</sub> receptor (SEQ ID NO:1) described above. was tested for efficacy in an in vitro model utilizing lung adenocarcinoma cells HTB-54. HTB-54 lung adenocarcinoma cells were demonstrated to express the A<sub>1</sub> adenosine receptor using standard northern blotting procedures and receptor probes designed and synthesized in the laboratory.

35 HTB-54 human lung adenocarcinoma cells (106/100 mm tissue culture dish) were exposed to 5.0  $\mu$ M HAdAlAS or HAdAlMM1 for 24 hours, with a fresh change of media and oligonucleotides after 12 hours of incubation. Following 24 hour exposure to the oligonucleotides, cells were harvested and their RNA extracted by standard procedures. A 21-mer probe corresponding to the region of mRNA targeted by the anti-sense (and therefore

having the same sequence as the anti-sense, but not phosphorothioated) was synthesized and used to probe northern blots of RNA prepared from HAdA1AS-treated, HAdA1MM1-treated and non-treated HTB-54 cells. These blots showed clearly that HAdA1AS but not HAdA1MM1 effectively reduced human adenosine receptor mRNA by >50%. This result showed that HAdA1AS is a good candidate for an anti-asthma drug since it depletes intracellular mRNA for the adenosine A<sub>1</sub> receptor, which is involved in asthma.

**Example 3: In Vivo Efficacy of Adenosine A<sub>1</sub> Receptor Anti-sense Oligos**

A fortuitous homology between the rabbit and human DNA sequences within the adenosine A<sub>1</sub> gene overlapping the initiation codon permitted the use of the phosphorothioate anti-sense oligonucleotides initially designed for use against the human adenosine A<sub>1</sub> receptor in a rabbit model.

Neonatal New Zealand white Pasteurella-free rabbits were immunized intraperitoneally within 24 hours of birth with 312 antigen units/ml house dustmite (*D. farinae*) extract (Berkeley Biologicals, Berkeley, CA), mixed with 10% kaolin. Immunizations were repeated weekly for the first month and then biweekly for the next 2 months. At 3-4 months of age, eight sensitized rabbits were anesthetized and relaxed with a mixture of ketamine hydrochloride (44 mg/kg) and acepromazine maleate (0.4 mg/kg) administered intramuscularly.

The rabbits were then laid supine in a comfortable position on a small molded, padded animal board and intubated with a 4.0-mm intratracheal tube (Mallinkrodt, Inc., Glens Falls, NY). A polyethylene catheter of external diameter 2.4 mm with an attached latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiments. The intratracheal tube was attached to a heated Fleisch pneumotachograph (size 00; DOM Medical, Richmond, VA), and flow was measured using a Validyne differential pressure transducer (Model DP-45161927; Validyne Engineering Corp., Northridge, CA) driven by a Gould carrier amplifier (Model 11-4113; Gould Electronic, Cleveland, OH). The esophageal balloon was attached to one side of the differential pressure transducer, and the outflow of the intratracheal tube was connected to the opposite side of the pressure transducer to allow recording of transpulmonary pressure. Flow was integrated to give a continuous tidal volume, and measurements of total lung resistance (RL) and dynamic compliance (C<sub>dyn</sub>) were calculated at isovolumetric and flow zero points, respectively, using an automated respiratory analyzer (Model 6; Buxco, Sharon, CT).

Animals were randomized and on Day 1 pretreatment values for PC50 were obtained for aerosolized adenosine. Anti-sense (HAdA1AS) or mismatched control (HAdA1MM) oligonucleotides were dissolved in sterile physiological saline at a concentration of 5000 µg

(5 mg) per 1.0 ml. Animals were subsequently administered the aerosolized anti-sense or mismatch oligonucleotide via the intratracheal tube (approximately 5000  $\mu$ g in a volume of 1.0 ml), twice daily for two days. Aerosols of either saline, adenosine, or anti-sense or mismatch oligonucleotides were generated by an ultrasonic nebulizer (DeVilbiss, Somerset, PA),  
5 producing aerosol droplets 80% of which were smaller than 5  $\mu$ m in diameter.

In the first arm of the experiment, four randomly selected allergic rabbits were administered anti-sense oligonucleotide and four the mismatched control oligonucleotide. On the morning of the third day, PC50 values (the concentration of aerosolized adenosine in mg/ml required to reduce the dynamic compliance of the bronchial airway 50% from the  
10 baseline value) were obtained and compared to PC50 values obtained for these animals prior to exposure to oligonucleotide.

Following a 1 week interval, animals were crossed over, with those previously administered mismatch control oligonucleotide now administered anti-sense oligonucleotide, and those previously treated with anti-sense oligonucleotide now administered mismatch  
15 control oligonucleotide. Treatment methods and measurements were identical to those employed in the first arm of the experiment. It should be noted that in six of the eight animals treated with anti-sense oligonucleotide, adenosine-mediated bronchoconstriction could not be obtained up to the limit of solubility of adenosine, 20 mg/ml. For the purpose of calculation, PC50 values for these animals were set at 20 mg/ml. The values given therefore represent a  
20 minimum figure for anti-sense effectiveness. Actual effectiveness was higher. The results of this experiment are illustrated in Table 3 below.

**Table 3:** Effect of Adenosine A<sub>1</sub> Receptor Anti-sense Oligo upon PC50 Values in Asthmatic Rabbits

Mismatch Control		A <sub>1</sub> Receptor Anti-sense Oligo	
Pre Oligonucleotide	Post Oligonucleotide	Pre Oligonucleotide	Post Oligonucleotide
3.56 ± 1.02	5.16 ± 1.03	2.36 ± 0.68	> 19.5 ± 0.34**

The results are presented as the mean (n=8) ± SEM.

The significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected test.

\*\*Significantly different from all other groups, p<0.01.

In both arms of the experiment, animals receiving the anti-sense oligonucleotide showed an order of magnitude increase in the dose of aerosolized adenosine required to reduce dynamic compliance of the lung by 50%. No effect of the mismatched control oligonucleotide upon PC50 values was observed. No toxicity was observed in any animal receiving either anti-sense or control inhaled oligonucleotide.

These results show clearly that the lung has exceptional potential as a target for anti-sense oligonucleotide-based therapeutic intervention in lung disease. They further show, in a model system which closely resembles human asthma, that downregulation of the adenosine A<sub>1</sub> receptor largely eliminates adenosine-mediated bronchoconstriction in asthmatic airways. Bronchial hyperresponsiveness in the allergic rabbit model of human asthma is an excellent endpoint for anti-sense intervention since the tissues involved in this response lie near to the point of contact with aerosolized oligonucleotides, and the model closely simulates an important human disease.

#### **Example 4: Specificity of A<sub>1</sub>-adenosine Receptor Anti-sense Oligonucleotide**

At the conclusion of the cross-over experiment of Example 3 above, airway smooth muscle from all rabbits was quantitatively analyzed for adenosine A<sub>1</sub> receptor number. As a control for the specificity of the anti-sense oligonucleotide, adenosine A<sub>2</sub> receptors, which should not have been affected, were also quantified.

Airway smooth muscle tissue was dissected from each rabbit and a membrane fraction prepared according to the method of Kleinstein et al. (Kleinstein, J. and Glossmann, H., Naunyn-Schmiedeberg's Arch. Pharmacol. 305: 191-200 (1978)), the relevant portion of which is hereby incorporated in its entirety by reference, with slight modifications. Crude plasma membrane preparations were stored at 70°C until the time of assay. Protein content was determined by the method of Bradford (M. Bradford, Anal. Biochem. 72, 240-254 (1976), the relevant portion of which is hereby incorporated in its entirety by reference). Frozen plasma



membranes were thawed at room temperature and were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37°C to remove endogenous adenosine. The binding of [<sup>3</sup>H] DPCPX (A<sub>1</sub> receptor-specific) or [<sup>3</sup>H] CGS-21680 (A<sub>1</sub> receptor-specific) was measured as previously described by Ali et al. (Ali, S. et al., J. Pharmacol. Exp. Ther. 268, Am. J. Physiol 5 266, L271-277 (1994), the relevant portion of which is hereby incorporated in its entirety by reference).

The animals treated with adenosine A<sub>1</sub> anti-sense oligonucleotide in the cross-over experiment had a nearly 75% decrease in A<sub>1</sub> receptor number compared to controls, as assayed by specific binding of the A<sub>1</sub>-specific antagonist DPCPX. There was no change in adenosine 10 A<sub>2</sub> receptor number, as assayed by specific binding of the A<sub>2</sub> receptor-specific agonist 2- [p-(2-carboxyethyl)-phenethylamino] -5' - (N-ethylcarboxamido) adenosine (CGS-21680). This is illustrated in Table 4 below.

**Table 4: Specificity of Action of Adenosine A<sub>1</sub> Receptor Anti-sense Oligonucleotide**

	Mismatch Control Oligonucleotide	A <sub>1</sub> Anti-sense Oligonucleotide
A <sub>1</sub> -Specific Binding	1105 ± 48**	293 ± 18
A <sub>2</sub> -Specific Binding	302 ± 22	442 ± 171

The results are presented as the mean (n = 8) ± SEM.

The significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected test.

\*\*Significantly different from mismatch control, p < 0.01.

The above results illustrate the effectiveness of anti-sense oligonucleotides in treating 25 airway disease. Since the anti-sense oligos described above. eliminate the receptor systems responsible for adenosine-mediated bronchoconstriction, it may be less imperative to eliminate adenosine from them. However, it would be preferable to eliminate adenosine from even these oligonucleotides to reduce the dose needed to attain a similar effect. Described above are other anti-sense oligonucleotides targeting mRNA of proteins involved in inflammation. Adenosine 30 has been eliminated from their nucleotide content to prevent its liberation during degradation.

#### **Example 5: Anti-sense Oligos directed to other Target Nucleic Acids**

This work was conducted to demonstrate that the present invention is broadly applicable to anti-sense oligonucleotides ("oligos") specific to nucleic acid targets broadly. The following experimental studies were conducted to show that the method of the invention is broadly 35 suitable for use with anti-sense oligos designed as taught by this application and targeted to any

and all adenosine receptor mRNAs. For this purpose, various anti-sense oligos were prepared to adenosine receptor mRNAs exemplified by the adenosine A<sub>1</sub>, A<sub>2b</sub> and A<sub>3</sub> receptor mRNAs.

Anti-sense Oligo I was disclosed above (SEQ. ID NO:1). Five additional anti-sense phosphorothioate oligos were designed and synthesized as indicated above.

- 5 1- Oligo II (SEQ. ID NO: 7) also targeted to the adenosine A<sub>1</sub> receptor, but to a different region than Oligo I.
- 2- Oligo V (SEQ. ID NO: 10) targeted to the adenosine A<sub>2b</sub> receptor.
- 3- Oligos III (SEQ. ID NO: 8) and IV (SEQ. ID NO: 9) targeted to different regions of the adenosine A<sub>3</sub> receptor.
- 10 4- Oligo I-PD (SEQ. ID NO: 1681)(a phosphodiester oligo of the same sequence as Oligo I).

These anti-sense oligos were designed for therapy on a selected species as described above and are generally specific for that species, unless the segment of the target mRNA of other species happens to contain a similar sequences. All anti-sense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and allergy, which have breathing difficulties and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application.

#### **Example 6: Design & Sequences of other Anti-sense Oligos**

Six oligos and their effects in a rabbit model were studied and the results of these studies are reported and discussed below. Five of these oligos were selected for this study to complement the data on Oligo I (SEQ ID NO: 1) provided in Examples 1 to 4 above. This oligo is anti-sense to one region of the adenosine A<sub>1</sub> receptor mRNA.

The oligos tested are identified as anti-sense Oligos I (SEQ ID NO: 1) and II (SEQ. ID No: 7) targeted to a different region of the adenosine A<sub>1</sub> receptor mRNA, Oligo V (SEQ. ID No:8) targeted to the adenosine A<sub>2b</sub> receptor mRNA, and anti-sense Oligos III and IV (SEQ. ID NOS: 9 and 10) targeted to two different regions of the adenosine A<sub>3</sub> receptor mRNA. The sixth oligo (Oligo I-PD) is a phosphodiester version of Oligo I (SEQ. ID NO:1). The design and synthesis of these anti-sense oligos was performed in accordance with Example 1 above.

#### **(I) Anti-sense Oligo I**

The anti-sense oligonucleotide I referred to in Examples 1 to 4 above is targeted to the human A<sub>1</sub> adenosine receptor mRNA (EPI 2010). Anti-sense oligo I is 21 nucleotide long, overlaps the initiation codon, and has the following sequence.

5'- GAT GGA GGG CGG CAT GGC GGG -3' (:SEQ. ID No 1)

The oligo I was previously shown to abrogate the adenosine-induced bronchoconstriction in allergic rabbits, and to reduce allergen-induced airway obstruction and

bronchial hyperresponsiveness (BHR), as discussed above and shown by Nyce, J. W. & Metzger, W. J., Nature, 385:721 (1977), the relevant portions of which reference are incorporated in their entireties herein by reference.

**(II) Anti-sense Oligo II**

5 A phosphorothioate anti-sense oligo (SEQ. ID NO:7) was designed in accordance with the invention to target the rabbit adenosine A<sub>1</sub> receptor mRNA region +936 to +956 relative to the initiation codon (start site). The anti-sense oligo II is 21 nucleotide long, and has the following sequence.

5'-CTC GTC GCC GTC GCC GGC GGG-3' (SEQ. ID NO:7)

10 **(III) Anti-sense Oligo III**

A phosphorothioate anti-sense oligo other than that provided in Example 1 above (SEQ. ID NO:8) was designed in accordance with the invention to target the anti-sense A<sub>3</sub> receptor mRNA region +3 to +22 relative to the initiation codon start site. The anti-sense oligo III is 20 nucleotide long, and has the following sequence.

15 5'-GGG TGG TGC TAT TGT CGG GC-3' (SEQ. ID NO:8)

**(IV) Anti-sense Oligo IV**

Yet another phosphorothioate anti-sense oligo (SEQ. ID NO:9) was designed in accordance with the invention to target the adenosine A<sub>3</sub> receptor mRNA region +386 to +401 relative to the initiation codon (start site). The anti-sense oligo IV is 15 nucleotide long, and has the following sequence.

5'-GGC CCA GGC CCA GCC-3' (SEQ. ID NO:9)

**(V) Anti-sense Oligo V**

A phosphorothioate anti-sense oligo (SEQ. ID NO:10) was designed in accordance with the invention to target the adenosine A<sub>2b</sub> receptor mRNA region -21 to -1 relative to the initiation codon (start site). The anti-sense oligonucleotide V is 21 nucleotide long, and has the following sequence.

5'-GGC CGG GCC AGC CGG GCC CGG-3' (SEQ. ID NO:10)

**(VI) A<sub>1</sub> Mismatch Oligos**

Two different mismatched oligonucleotides having the following sequences were used as controls for anti-sense oligo I (SEQ. ID NO: 1) described in Example 5 above.

A<sub>1</sub> MM2 5'-GTA GGT GGC GGG CAA GGC GGG-3' (SEQ. ID NO:1682)

A<sub>1</sub> MM3 5'-GAT GGA GGC GGG CAT GGC GGG-3' (SEQ. ID NO:1683)

Anti-sense oligo I and the two mismatch anti-sense oligos had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligo I was specific, not only for the human, but also for the rabbit, adenosine A<sub>1</sub> receptor genes, and that the mismatched controls were not candidates for hybridization with any known human or animal gene sequence.

**(VII) Anti-sense Oligo A<sub>1</sub>-PD (Oligo VI)**

A phosphodiester anti-sense oligo (Oligo VI; SEQ. ID NO:1681) having the same nucleotide sequence as Oligo I was designed as disclosed in the above-identified application. Anti-sense oligo I-PD is 21 nucleotide long, overlaps the initiation codon, and has the following sequence.

5'- GAT GGA GGG CGG CAT GGC GGG -3' (SEQ. ID NO:1681)

**III) Controls**

Each rabbit was administered 5.0 ml aerosolized sterile saline following the same schedule as for the anti-sense oligos in (II), (III), and (IV) above.

**10    Example 7: Synthesis of Anti-sense Oligos**

Phosphorothioate anti-sense oligos having the sequences described in (a) above, were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, DE). TETD (tetraethylthiuram disulfide) was used as the sulfurizing agent during the synthesis. Anti-sense oligonucleotide II (SEQ. ID NO:7), anti-sense oligonucleotide III (SEQ. ID NO: 8) and anti-sense oligonucleotide IV (SEQ. ID NO: 9) were each synthesized and purified in this manner.

**Example 8: Preparation of Allergic Rabbits**

Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (*D. farinae*) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp. 347-362, CRC Press, Boca Raton (1990); Ali, S., Metzger, W. J. and Mustafa, S. J., Am. J. Resp. Crit. Care Med. 149: 908 (1994)), the relevant portions of which are incorporated in their entirety here by reference. Immunizations were repeated weekly for the first month and then biweekly until the age of 4 months. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of allergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (Ali, S., Metzger, W. J. and Mustafa, S. J., Am. J. Resp. Crit. Care Med. 149 (1994)), the relevant section being incorporated in its entirety here by reference.

**DOSE-RESPONSE STUDIES**

**Example 9: Experimental Setup**

Aerosols of either adenosine (0-20 mg/ml), or anti-sense or one of two mismatch oligonucleotides (5 mg/ml) were separately prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerset, PA), which produced aerosol droplets, 80% of which were smaller than 5 $\mu$ m in diameter. Equal volumes of the aerosols were administered directly to the lungs *via* an intratracheal tube.

The animals were randomized, and administered aerosolized adenosine. Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC<sub>50</sub> Adenosine). The animals were then administered either the aerosolized anti-sense or one of the mismatch anti-sense oligos via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2 days (total dose, 20 mg). Post-treatment PC<sub>50</sub> values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in Example 21 below.

**Example 10: Crossover Experiments**

For some experiments utilizing anti-sense oligo I (SEQ ID NO: 1) and a corresponding mismatch control oligonucleotide A1MM2, following a 2 week interval, the animals were crossed over, with those previously administered the mismatch control A<sub>1</sub>MM2, now receiving the anti-sense oligo I, and those previously treated with the anti-sense oligo I, now receiving the mismatch control A<sub>1</sub>MM2 oligo.

The number of animals per group was as follows. For mismatch A<sub>1</sub>MM2 (Control 1), n=7, since one animal was lost in the second control arm of the experiment due to technical difficulties, for mismatch A<sub>1</sub>MM3 n=4 (Control 2) and for A<sub>1</sub>AS anti-sense oligo I, n=8. The A<sub>1</sub>MM3 oligo-treated animals were analyzed separately and were not part of the cross-over experiment. The treatment methods and measurements employed following the cross-over were identical to those employed in the first arm of the experiment.

In 6 of the 8 animals treated with the anti-sense oligo I (SEQ. ID NO: 1), no PC<sub>50</sub> value could be obtained for adenosine doses of up to 20 mg/ml, which is the limit of solubility of adenosine. Accordingly, the PC<sub>50</sub> values for these animals were assumed to be 20 mg/ml for calculation purposes. The values given, therefore, represent a minimum figure for the effectiveness of the anti-sense oligonucleotides of the invention. Other groups of allergic rabbits (n=4 for each group) were administered 0.5 or 0.05 mg doses of the anti-sense oligo I (SEQ ID NO: 1), or the A<sub>1</sub>MM2 oligo in the manner and according to the schedule described above (the total doses being 2.0 or 0.2 mg). The results of these studies are provided in Example 22 below.

**Example 11: Anti-sense Oligo Formulation**

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I (SEQ. ID N :1) in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above.

- 5        The results obtained for anti-sense oligo I and its mismatch controls confirmed that the mismatch controls are equivalent to saline, as described in Example 19 below and in Table 1 of Nyce & Metzger, Nature 385, 721-725 (1997). Because of this finding, saline was used as a control for pulmonary function studies employing anti-sense oligos II, III and IV (SEQ. IS NOS; 7, 8 and 9).

10    **Example 12: Specificity of Oligo I for Adenosine A<sub>1</sub> Receptor (Receptor Binding Studies)**

- Tissue from airway smooth muscle was dissected to primary, secondary and tertiary bronchi from rabbits which had been administered 20 mg oligo I (SEQ ID NO: 1) in 4 divided doses over a period of 48 hours as described above. A membrane fraction was prepared according to the method of Ali et al. (Ali, S., et al., Am. J. Resp. Crit. Care Med. 149: 908  
15 (1994), the relevant section relating to the preparation of the membrane fraction is incorporated in its entirety hereby by reference).

- The protein content was determined by the method of Bradford and plasma membranes were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37°C to remove endogenous adenosine. See, Bradford, M. M. Anal. Biochem. 72, 240-254 (1976), the  
20 relevant portion of which is hereby incorporated in its entirety by reference. The binding of [<sup>3</sup>H]DPCPX, [<sup>3</sup>H]NPC17731, or [<sup>3</sup>H]CGS-21680 was measured as described by Jarvis et al. See, Jarvis, M.F., et al., Pharmacol. Exptl. Ther. 251, 888-893 (1989), the relevant portion of which is fully incorporated herein by reference. The results of this study are shown in Table 8 and discussed in Example 20 below.

25    **Example 13: Pulmonary Function Measurements**  
(Compliance c<sub>DYN</sub> and Resistance)

- At 4 months of age, the immunized animals were anesthetized and relaxed with 1.5 ml of a mixture of ketamine HCl (35 mg/kg) and acepromazine maleate (1.5 mg/kg) administered intramuscularly. After induction of anesthesia, allergic rabbits were comfortably positioned  
30 supine on a soft molded animal board. Salve was applied to the eyes to prevent drying, and they were closed. The animals were then intubated with a 4.0 mm intermediate high-low cuffed Murphy 1 endotracheal tube (Mallinckrodt, Glen Falls, NY), as previously described by Zavala and Rhodes. See, Zavala and Rhodes, Proc. Soc. Exp. Biol. Med. 144: 509-512

(1973), the relevant portion of which is incorporated herein by reference in its entirety. A polyethylene catheter of OD 2.4 mm (Becton Dickinson, Clay Adams, Parsippany NJ) with an attached thin-walled latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiment. The endotracheal tube was attached to a heated Fleisch pneumotach (size 00; DEM Medical, Richmond, VA), and the flow ( $v$ ) measured using a Validyne differential pressure transducer (Model DP-45-16-1927, Validyne Engineering, Northridge, CA), driven by a Gould carrier amplifier (Model 11-4113, Gould Electronics, Cleveland, OH).

An esophageal balloon was attached to one side of the Validyne differential pressure transducer, and the other side was attached to the outflow of the endotracheal tube to obtain transpulmonary pressure ( $P_p$ ). The flow was integrated to yield a continuous tidal volume, and the measurements of total lung resistance ( $R_t$ ) and dynamic compliance ( $C_{dyn}$ ) were made at isovolumetric and zero flow points. The flow, volume and pressure were recorded on an eight channel Gould 2000 W high-frequency recorder and  $C_{dyn}$  was calculated using the total volume and the difference in  $P_p$  at zero flow, and  $R_t$  was calculated as the ratio of  $P_{tp}$  and  $V$  at midtidal lung volumes. These calculations were made automatically with the Buxco automated pulmonary mechanics respiratory analyzer (Model 6, Buxco Electronics, Sharon, CT), as previously described by Giles et al. See, Giles et al., Arch. Int. Pharmacodyn. Ther. 194: 213-232 (1971), the relevant portion of which describing these calculations is incorporated in toto hereby by reference. The results obtained upon administration of oligo II on allergic rabbits are shown and discussed in Example 26 below.

#### **Example 14: Measurement of Bronchial Hyperresponsiveness (BHR)**

Each allergic rabbit was administered histamine by aerosol to determine their baseline hyperresponsiveness. Aerosols of either saline or histamine were generated using a DeVilbiss nebulizer (DeVilbiss, Somerset, PA) for 30 seconds and then for 2 minutes at each dose employed. The ultrasonic nebulizer produced aerosol droplets of which 80% were <5 micron in diameter. The histamine aerosol was administered in increasing concentrations (0.156 to 80 mg/ml) and measurements of pulmonary function were made after each dose. The B4R was then determined by calculating the concentration of histamine (mg/ml) required to reduce the  $C_{dyn}$  50% from baseline ( $PC_{50}$  Histamine).

#### **Example 15: Cardiovascular Effect of Anti-sense Oligo I**

The measurement of cardiac output and other cardiovascular parameters using Cardiomax™ utilizes the principal of thermal dilution in which the change in temperature of the blood exiting the heart after a venous injection of a known volume of cool saline is monitored. A single rapid injection of cool saline was made into the right atrium via cannulation of the

right jugular vein, and the corresponding changes in temperature of the mixed injectate and blood in the aortic arch were recorded via cannulation of the carotid artery by a temperature-sensing miniprobe.

Twelve hours after the allergic rabbits had been treated with aerosols of oligo I (EPI 2010; SEQ. ID NO: 1) as described in (d) above, the animals were anesthetized with 0.3 ml/kg of 80% Ketamine and 20% Xylazine. This time point coincides with previous data showing efficacy for SEQ. ID NO: 1, as is clearly shown by Nyce & Metzger, (1997), supra, the pertinent disclosure being incorporated in its entirety here by reference. A thermocouple was then inserted into the left carotid artery of each rabbit, and was then advanced 6.5 cm and secured with a silk ligature. The right jugular vein was then cannulated and a length of polyethylene tubing was inserted and secured.

A thermodilution curve was then established on a Cardiomax™ II (Columbus Instruments, Ohio) by injecting sterile saline at 20°C to determine the correctness of positioning of the thermocouple probe. After establishing the correctness of the position of the thermocouple, the femoral artery and vein were isolated. The femoral vein was used as a portal for drug injections, and the femoral artery for blood pressure and heart rate measurements. Once constant baseline cardiovascular parameters were established, Cardiomax™ measurements of blood pressure, heart rate, cardiac output, total peripheral resistance, and cardiac contractility were made.



**Example 16: Duration of Action of Oligo I**  
(SEQ. ID NO: 1)

Eight allergic rabbits received initially increasing log doses of adenosine by means of a nebulizer via an intra-tracheal tube as described in (f) above, beginning with 0.156 mg/ml until compliance was reduced by 50% ( $PC_{50}$  Adenosine) to establish a baseline. Six of the rabbits then received four 5 mg aerosolized doses of (SEQ. ID NO: 1) as described above. Two rabbits received equivalent amounts of saline vehicle as controls. Beginning 18 hours after the last treatment, the  $PC_{50}$  Adenosine values were tested again. After this point, the measurements were continued for all animals each day, for up to 10 days. The results of this study are discussed in Example 25 below.

**Example 17: Reduction of Adenosine  $A_{2b}$  Receptor**  
Number by Anti-sense Oligo V

Sprague Dawley rats were administered 2.0 mg respirable anti-sense oligo V (SEQ ID NO:10) three times over two days using an inhalation chamber as described above. Twelve hours after the last administration, lung parenchymal tissue was dissected and assayed for adenosine  $A_{2b}$  receptor binding using [311]-NECA as described by Nyce & Metzger (1997), supra. Controls were conducted by administration of equal volumes of saline. The results are significant at  $p < 0.05$  using Student's paired t test, and are discussed in Example 28 below.

**Example 18: Comparison of Oligo I & Corresponding**  
Phosphodiester Oligo VI (SEQ. ID NO:1681)

Oligo I (SEQ ID NO:1) countered the effects of adenosine and eliminated sensitivity to it for adenosine amounts up to 20 mg adenosine/5.0 ml (the limit of solubility of adenosine). Oligo VI (SEQ ID NO:1681), the phosphodiester version of the oligonucleotide sequence, was completely ineffective when tested in the same manner. Both compounds have identical sequence, differing only in the presence of phosphorothioate residues in Oligo I (SEQ ID NO:1), and were delivered as an aerosol as described above and in Nyce & Metzger (1997), supra. Significantly different at  $p < 0.001$ , Student's paired t test. The results are discussed in Example 29 below..

**30 RESULTS OBTAINED FOR ANTI-SENSE OLIGO I (SEQ. ID NO: 1)**

**Example 19: Results of Prior Work**

The nucleotide sequence and other data for anti-sense oligo I (SEQ. ID NO: 1), which is

specific for the adenosine A<sub>1</sub> receptor, were provided above. The experimental data showing the effectiveness of oligo I in down regulating the receptor number and activity were also provided above.

Further information on the characteristics and activities of anti-sense oligo I is provided in Nyce, J. W. and Metzger, W. J., Nature 385:721 (1997), the relevant parts of which relating to the following results are incorporated in their entirety herein by reference. The Nyce & Metzger (1997) publication provided data showing that the anti-sense oligo I (SEQ. ID NO: 1):

(1) The anti-sense oligo I reduces the number of adenosine A<sub>1</sub> receptors in the bronchial smooth muscle of allergic rabbits in a dose-dependent manner as may be seen in Table 5 below.

(2) Anti-sense Oligo I attenuates adenosine-induced bronchoconstriction and allergen-induced bronchoconstriction.

(3) The Oligo I attenuates bronchial hyperresponsiveness as measured by PC<sub>50</sub> histamine, a standard measurement to assess bronchial hyperresponsiveness. This result clearly demonstrates anti-inflammatory activity of the anti-sense oligo I as is shown in Table 5 above.

(4) As expected, because it was designed to target it, the anti-sense oligo I is totally specific for the adenosine A<sub>1</sub> receptor, and has no effect at all at any dose on either the very closely related adenosine A<sub>2</sub> receptor or the related bradykinin B<sub>2</sub> receptor. This is seen in Table 5 below.

(5) In contradistinction to the above effects of the Oligo I, the mismatch control molecules MM2 and MM3 (SEQ. ID NO:1682 and SEQ. ID NO:1683) which have identical base composition and molecular weight but differed from the anti-sense oligo I (SEQ ID NO: 1) by 6 and 2 mismatches, respectively. These mismatches, which are the minimum possible while still retaining identical base composition, produced absolutely no effect upon any of the targeted receptors (A<sub>1</sub>, A<sub>2</sub> or B<sub>2</sub>).

These results, along with a complete lack of prior art on the use of anti-sense oligonucleotides, such as oligo I, targeted to the adenosine A<sub>1</sub> receptor, are unexpected results. The showings presented in this patent clearly enable and demonstrate the effectiveness, for their intended use, of the claimed agents and method for treating a disease or condition associated with lung airway, such as bronchoconstriction, inflammation, allergy(ies), and the like.

**Example 20: Oligo I Significantly Reduces  
Response to Adenosine Challenge**

The receptor binding experiment is described in Example 12 above, and the results shown in Table 5 below which shows the binding characteristics of the adenosine A<sub>1</sub>-selective ligand [<sup>3</sup>H]DPCPX and the bradykinin B<sub>2</sub>-selective ligand [<sup>3</sup>H]NPC 17731 in membranes isolated from airway smooth muscle of A<sub>1</sub> adenosine receptor and B<sub>2</sub> bradykinin receptor anti-sense- and mismatch-treated allergic rabbits.

5

**Table 5: Binding Characteristics of Three Anti-Sense Oligos**

Treatment <sup>1</sup>	A <sub>1</sub> receptor		B <sub>2</sub> receptor	
	Kd	B <sub>max</sub>	Kd	Bmax
<b>Adenosine A<sub>1</sub> Receptor</b>				
20 mg	0.36±0.029 nM	19±1.52 fmoles*	0.39±0.031 nM	14.8±0.99fmoles
2 mg	0.38±0.030 nM	32±2.56 fmoles*	0.41±0.028 nM	15.5±1.08 fmoles
0.2 mg	0.37±0.030 nM	49±3.43 fmoles	0.34±0.024 nM	15.0±1.06 fmoles
<b>A<sub>1</sub>MM1 (Control)</b>				
20 mg	0.34±0.027 nM	52.0±3.64 fmoles	0.35±0.024 nM	14.0±1.0 fmoles
2 mg	0.37±0.033 nM	51.8±3.88 fmoles	0.38±0.028 nM	14.6±1.02 fmoles
<b>B<sub>2</sub>A (Bradykinin Receptor)</b>				
20 mg	0.36±0.028 nM	45.0±3.15 fmoles	0.38±0.027 nM	8.7±0.62 fmoles*
2 mg	0.39±0.035 nM	44.3±2.90 fmoles	0.34±0.024 nM	11.9±0.76 fmoles**
0.2 mg	0.40±0.028 nM	47.0±3.76 fmoles	0.35±0.028 nM	15.1±1.05 fmoles
<b>B<sub>2</sub>MM (Control)</b>				
20 mg	0.39±0.031 nM	42.0±2.94 fmoles	0.41±0.029 nM	14.0±0.98 fmoles
2 mg	0.41±0.035 nM	40.0±3.20 fmoles	0.37±0.030 nM	14.8±0.99 fmoles
0.2 mg	0.37±0.029 nM	43.0±3.14 fmoles	0.36±0.025 nM	15.1±1.35 fmoles
<b>Saline Control</b>	0.37±0.041	46.0±5.21	0.39±0.047 nM	14.2±1.35 fmoles

<sup>1</sup> Refers to total oligo administered in four equivalently divided doses over a 48 hour period. Treatments and analyses were performed as described in methods. Significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected t test. n = 4-6 for all groups.

\* Significantly different from mismatch control- and saline-treated groups, p<0.001;

\*\*Significantly different from mismatch control- and saline-treated groups, p<0.05.

#### **Example 21: Dose-response Effect of Oligo I**

Anti-sense oligo I (SEQ ID NO:1) was found to reduce the effect of adenosine administration to the animal in a dose-dependent manner over the dose range tested as shown in Table 6 below.

**Table 6: Dose-Response Effect to Anti-sense Oligo I**

	Total Dose (mg)	PC <sub>50</sub> Adenosine (mg Adenosine)
5	<b>Anti-sense Oligo I</b>	
	0.2	8.32±7.2
	2.0	14.0±7.2
	20	19.5±0.34
10	<b>A<sub>1</sub>MM2 oligo (control)</b>	
	0.2	2.51±0.46
	2.0	3.13± 0.71
	20	3.25± 0.34
15	The above results were studied with the Student's paired t test and found to be statistically different, p=0.05	

The oligo I (SEQ. ID NO:1), an anti-adenosine A<sub>1</sub> receptor oligo, acts specifically on the adenosine A<sub>1</sub> receptor, but not on the adenosine A<sub>2</sub> receptors. These results stem from the treatment of rabbits with anti-sense oligo I (SEQ. ID NO:1) or mismatch control oligo (SEQ. ID NO:1682; A<sub>1</sub>MM2) as described in Example 9 above and in Nyce & Metzger (1997), supra (four doses of 5 mg spaced 8 to 12 hours apart via nebulizer via endotracheal tube), bronchial smooth muscle tissue excised and the number of adenosine A<sub>1</sub> and adenosine A<sub>2</sub> receptors determined as reported in Nyce & Metzger (1997), supra.

**Example 22: Specificity of Oligo I (SEQ. ID NO:1) for Target Gene Product**

Oligo I (SEQ. ID No:1) is specific for the adenosine A<sub>1</sub> receptor whereas its mismatch controls had no activity. Figure 1 depicts the results obtained from the cross-over experiment described in Example 10 above and in Nyce & Metzger (1997), supra. The two mismatch controls (SEQ. ID NO:1682 and SEQ. ID NO:1683) evidenced no effect on the PC<sub>50</sub> Adenosine value. On the contrary, the administration of anti-sense oligo I (SEQ. ID NO:1) showed a seven-fold increase in the PC<sub>50</sub> Adenosine value. The results clearly indicate that the anti-sense oligo I (SEQ. ID NO: 1) reduces the response (attenuates the sensitivity) to exogenously administered adenosine when compared with a saline control. The results provided in Table 2 above clearly establish that the effect of the anti-sense oligo I is dose dependent (see, column 3 of Table 1).

The Oligo I was also shown to be totally specific for the adenosine A<sub>1</sub> receptor, (see, top 3 rows of Table), inducing no activity at either the closely related adenosine A<sub>2</sub> receptor or the bradykinin B<sub>2</sub> receptor (see, lines 8-10 of Table 2 above).

In addition, the results shown in Table 2 establish that the anti-sense oligo I (SEQ. ID

NO:1) decreases sensitivity to adenosine in a dose dependent manner, and that it does this in an anti-sense oligo-dependent manner since neither of two mismatch control oligonucleotides ( $A_1$ MM2; SEQ. ID NO:1682 and  $A_1$ MM3; SEQ. ID NO:1683) show any effect on  $PC_{50}$  Adenosine values or on attenuating the number of adenosine  $A_1$  receptors.

5     **Example 23: Effect on Aeroallergen-induced  
Bronchoconstriction & Inflammation**

10     The Oligo I (SEQ. ID NO:1) was shown to significantly reduce the histamine-induced effect in the rabbit model when compared to the mismatch oligos. The effect of the anti-sense Oligo I (SEQ. ID No:1) and the mismatch oligos ( $A_1$ MM2, SEQ. ID NO:1682 and  $A_1$ MM3, SEQ. ID NO:1682) on allergen-induced airway obstruction and bronchial hyperresponsiveness was assessed in allergic rabbits.

15     The effect of the anti-sense oligo I (SEQ. ID NO:1) on allergen-induced airway obstruction was assessed. As calculated from the area under the plotted curve, the anti-sense oligo I significantly inhibited allergen-induced airway obstruction when compared with the mismatched control (55 %,  $p < 0.05$ ; repeated measures ANOVA, and Tukey's t test).

20     A complete lack of effect was induced by the mismatch oligo  $A_1$ MM2 (Control) on allergen induced airway obstruction.

25     The effect of the anti-sense oligo I (SEQ. ID NO:1) on allergen-induced BHR was determined as above. As calculated from the  $PC_{50}$  Histamine value, the anti-sense oligo I (SEQ. ID NO:1) significantly inhibited allergen-induced BHR in allergic rabbits when compared to the mismatched control (61 %,  $p < 0.05$ ; repeated measures ANOVA, Tukey's t test).

30     A complete lack of effect of the  $A_1$ MM mismatch control on allergen-induced BHR was observed.

35     The results indicated that anti-sense oligo I (SEQ. ID NO: 1) is effective to protect against aeroallergen-induced bronchoconstriction (house dust mite). In addition, the anti-sense oligo I (SEQ. ID NO:1) was also found to be a potent inhibitor of dust mite-induced bronchial hyperresponsiveness, as shown by its effects upon histamine sensitivity which indicates anti-inflammatory activity for anti-sense oligo I (SEQ. ID NO:1).

40     **Example 24: Anti-sense Oligo I is Free  
of Deleterious Side Effects**

45     The Oligo I (SEQ. ID NO:1) was shown to be free of side effects that might be toxic to the recipient. No changes in arterial blood pressure, cardiac output, stroke volume, heart rate, total peripheral resistance or heart contractility (dPdT) were observed following administration of 2.0 or 20 mg oligo I (SEQ. ID NO:1). The addition, the results of the measurement of

cardiac output (CO), stroke volume (SV), mean arterial pressure (MAP), heart rate (HR), total peripheral resistance (TPR), and contractility (dPdT) with a Cardiomax™ apparatus (Columbus Instruments, Ohio) were assessed.

5 These results evidenced that oligo I (SEQ. ID NO:1) has no detrimental effect upon critical cardiovascular parameters. More particularly, this oligo does not cause hypotension. This finding is of particular importance because other phosphorothioate anti-sense oligonucleotides have been shown in the past to induce hypotension in some model systems. Furthermore, the adenosine A<sub>1</sub> receptor plays an important role in sinoatrial conduction within the heart. Attenuation of the adenosine A<sub>1</sub> receptor by anti-sense oligo I (SEQ. ID NO:1) might  
10 be expected to result, therefore, in deleterious extrapulmonary activity in response to the downregulation of the receptor. This is not the case. The anti-sense oligo I (SEQ. ID NO:1) does not produce any deleterious intrapulmonary effects and renders the administration of the low doses of the present anti-sense oligo free of unexpected, undesirable side effects.

15 This demonstrates that when oligo I (SEQ. ID NO:1) is administered directly to the lung, it does not reach the heart in significant quantities to cause deleterious effects. This is in contrast to traditional adenosine receptor antagonists like theophylline which do escape the lung and can cause deleterious, even life-threatening effects outside the lung.

#### **Example 25: Long Lasting Effect of Oligo I**

20 The Oligo I (SEQ. ID NO:1) evidenced a long lasting effect as evidenced by the PC<sub>50</sub> and Resistance values obtained upon its administration prior to adenosine challenge.

The duration of the effect was measured for with respect to the PC<sub>50</sub> of adenosine anti-sense oligo I when administered in four equal doses of 5 mg each by means of a nebulizer via an endotracheal tube, as described above. The effect of the agent is significant over days 1 to 8 after administration. When the effect of the anti-sense oligo I (SEQ. ID NO:1) had  
25 disappeared, the animals were administered saline aerosols (controls), and the PC<sub>50</sub> Adenosine values for all animals were measured again. Saline-treated animals showed base line PC<sub>50</sub> adenosine values (n=6).

The duration of the effect (with respect to Resistance) was measured for six allergic rabbits which were administered 20 mg of anti-sense oligo I (SEQ. ID NO: 1) as described  
30 above, upon airway resistance measured as also described above. The mean calculated duration of effect was 8.3 days for both PC<sub>50</sub> adenosine (p < 0.05) and resistance (p < 0.05). These results show that anti-sense oligo I (SEQ. ID NO:1) has an extremely long duration of action, which is completely unexpected.

#### **Example 26: Anti-sense Oligo II**

Anti-sense oligo II, targeted to a different region of the adenosine A<sub>1</sub> receptor mRNA, was found to be highly active against the adenosine A<sub>1</sub>-mediated effects. The experiment measured the effect of the administration of anti-sense oligo II (SEQ. ID NO:7) upon compliance and resistance values when 20 mg anti-sense oligo II or saline (control) were administered to two groups of allergic rabbits as described above. Compliance and resistance values were measured following an administration of adenosine or saline as described above in Example 13. The effect of the anti-sense oligo of the invention was different from the control in a statistically significant manner,  $p < 0.05$  using paired t-test, compliance;  $p < 0.01$  for resistance.

The results showed that anti-sense oligo II (SEQ. ID NO:7), which targets the adenosine A<sub>1</sub> receptor, effectively maintains compliance and reduces resistance upon adenosine challenge.

#### **Example 27: Antisense Oligos III and IV**

Oligos III (SEQ. ID NO:8) and IV (SEQ. ID NO:9) were shown to be in fact specifically targeted to the adenosine A<sub>3</sub> receptor by their effect on reducing inflammation and the number of inflammatory cells present upon separate administration of 20 mg of the anti-sense oligos III (SEQ. ID NO:8) and IV (SEQ. ID NO:9) to allergic rabbits as described above. The number of inflammatory cells was determined in their bronchial lavage fluid 3 hours later by counting at least 100 viable cells per lavage.

The effect of anti-sense oligos III (SEQ. ID NO:8) and IV (SEQ. ID NO:9) upon granulocytes, and upon total cells in bronchial lavage were assessed following exposure to dust mite allergen. The results showed that the anti-sense oligo IV (SEQ. ID NO:9) and anti-sense oligo III (SEQ. ID NO:8) are very potent anti-inflammatory agents in the asthmatic lung following exposure to dust mite allergen. As is known in the art, granulocytes, especially eosinophils, are the primary inflammatory cells of asthma, and the administration of anti-sense oligos III (SEQ. ID NO:8) and IV (SEQ. ID NO:9) reduced their numbers by 40% and 66%, respectively. Furthermore, anti-sense oligos IV (SEQ. ID NO:9) and III (SEQ. ID NO:8) also reduced the total number of cells in the bronchial lavage fluid by 40% and 80%, respectively. This is also an important indicator of anti-inflammatory activity by the present anti-adenosine A<sub>3</sub> agents of the invention. Inflammation is known to underlie bronchial hyperresponsiveness and allergen-induced bronchoconstriction in asthma. Both anti-sense oligonucleotides III (SEQ. ID NO:8) and IV (SEQ. ID NO:9), which are targeted to the adenosine A<sub>3</sub> receptor, are representative of an important new class of anti-inflammatory agents which may be designed to specifically target the lung receptors of each species.

#### **Example 28: Anti-sense Oligo V**

The anti-sense oligo V (SEQ. ID NO:10), targeted to the adenosine A<sub>2b</sub> adenosine receptor mRNA was shown to be highly effective at countering adenosine A<sub>2b</sub>-mediated effects



and at reducing the number of adenosine A<sub>2b</sub> receptors present to less than half.

**Example 29: Unexpected Superiority of Substituted  
over Phosphodiester-residue Oligo I-DS  
(SEQ. ID NO:1681)**

5           Oligos I (SEQ. ID NO:1) and I-DS (SEQ. ID NO:1681) were separately administered to allergic rabbits as described above, and the rabbits were then challenged with adenosine. The phosphodiester oligo I-DS (SEQ. ID NO:1681) was statistically significantly less effective in countering the effect of adenosine whereas oligo I (SEQ. ID NO:1) showed high effectiveness, evidencing a PC<sub>50 Adenosine</sub> of 20 mg.

10       **Example 30: Anti-sense Oligo VI**

          For the present work, I designed an additional anti-sense phosphorothioate oligo targeted to the adenosine A<sub>1</sub> receptor (Oligo VI). This anti-sense oligo was designed for therapy on a selected species as described in the above patent application and is generally specific for that species, unless the segment of the adenosine receptor mRNA of other species elected happens to have a similar sequence. The anti-sense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and lung allergy, which have breathing difficulties and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application.

          One additional oligo and its effect in a rabbit model was studied and the results of the study are reported and discussed below. The present oligo (anti-sense oligo VI) was selected for this study to complement the data on SEQ ID NO: 1 (Oligo I), which is anti-sense to the adenosine A<sub>1</sub> receptor mRNA provided in the above-identified patent application. This additional oligo is identified as anti-sense Oligo VI, and is targeted to a different region of the adenosine A<sub>1</sub> receptor mRNA than Oligo I. The design and synthesis of this anti-sense oligo was performed in accordance with the teaching, particularly Example 1, of the above-identified patent application.

25           The anti-sense Oligo VI is a phosphorothioate designed to target the coding region of the rabbit adenosine A<sub>1</sub> receptor mRNA region +964 to +984 relative to the initiation codon (start site). The Oligo VI was prepared as described in the above-indicated application, and is 20 nucleotides long. The Oligo VI is directed to the adenosine A<sub>1</sub> receptor gene, and has the following sequence.

          5'-CGC CGG CGG GTG CGG GCC GG-3' (SEQ. ID NO: )

30           The phosphorothioate anti-sense Oligo VI having the sequence described in (5) above, was synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, DE). TETD (tetraethylthiuram disulfide) was used as the sulfurizing agent during the synthesis.

**Example 31: Preparation of Allergic Rabbits**

35           Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (*D. farinae*) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp 347-362, CRC Press, Boca Raton,

1990; Ali, S. Et al., Am. J. Resp. Crit. Care Med. 149: 908 (1994)).

The immunizations were repeated weekly for the first month and then bi-weekly until the animals were 4 months old. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of allergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (1994), supra.

#### **Example 32: Adenosine Aerosol Preparation**

10 An adenosine aerosol (20 mg/ml) was prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerset, PA), which produced aerosol droplets, 80% of which were smaller than 5 $\mu$ m in diameter. Equal volumes of the aerosols were administered directly to the lungs via an intratracheal tube to all three rabbits.

The animals were then administered the aerosolized adenosine and Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC<sub>50</sub> Adenosine). The animals were then administered the aerosolized anti-sense via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2 days (total dose, 20 mg). Post-treatment PC<sub>50</sub> values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in (9) below.

#### **Example 33: Anti-sense Oligo Formulation**

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above.

#### **Example 34: Oligo VI Reduces Response to Adenosine Challenge as well or Better than Oligo I**

Oligo VI was tested in three allergic rabbits of the characteristics and readied as described in (7) above and in the above-indicated patent application. Oligo VI targets a section of the coding region of the A<sub>1</sub> receptor which is different from Oligo I. Both these target sequences were selected randomly from many possible coding region target sequences.

The three rabbits were treated identically as previously indicated for Oligo I. Briefly, 5 mg of Oligo VI were nebulized to the rabbits twice per day at 8 hour intervals, for two days. Thereafter, PC<sub>50</sub> adenosine studies were performed on the morning of the third day and compared to pre-treatment PC<sub>50</sub> values. This protocol is described in more detail in Nyce and Metzger (Nyce & Metzger, Nature 385: 721-725 (1997)).

The results obtained for the three rabbits are shown in Table 1 below.

**Table 1: PC<sub>50</sub> Aden sine before & after Aerosolized Adenosine Treatment**

Treatment Time	PC <sub>50</sub> Adenosine (mg)
----------------	---------------------------------

Pre-treatment	3.0 ± 2.1
Post-treatment	>20.0*

5

\* maximum achievable dose due to adenosine insolubility in saline

10

All three animals treated with Oligo VI completely eliminated sensitivity to adenosine up to the measurable level of the agent shown in Table 1 above. That is, the administration of the Oligo VI abrogated the adenosine-induced bronchoconstriction in the three allergic rabbits. The actual efficacy of Oligo VI is, therefore, greater than could be measured in the experimental system used.

By comparing with the previously submitted results for the Oligo I, it may be seen that the Oligo VI was found to be as effective, or more, than Oligo I.

#### **Example 34: Conclusions**

15

The work described and results discussed in the examples clearly indicates that all anti-sense oligonucleotides designed in accordance with the teachings of the above-identified application were found to be highly effective at countering or reducing effects mediated by the receptors they are targeted to. That is, each and all of the two anti-sense oligos targeting an adenosine A<sub>1</sub> receptor mRNA, 1 anti-sense oligo targeting an adenosine A<sub>2b</sub> receptor mRNA, and the 2 anti-sense oligos targeting an A<sub>3</sub> receptor mRNA were shown capable of countering the effect of exogenously administered adenosine which is mediated by the specific receptor they are targeted to.

20

The activity of the anti-sense oligos of this invention, moreover, is specific to the target and substitutively fails to inhibit another target.

25

In addition, the results presented also show that the administration of the present agents results in extremely low or non-existent deleterious side effects or toxicity.

This represents 100% success in providing agents that are highly effective and specific in the treatment of bronchoconstriction and/or inflammation. This invention is broadly applicable in the same manner to all gene(s) and corresponding mRNAs encoding proteins involved in or associated with airway diseases.

30

A comparison of the phosphodiester and a version of the same oligonucleotide wherein the phosphodiester bonds are substituted with phosphorothioate bonds evidenced an unexpected superiority for the phosphothiorate oligonucleotide over the phosphodiester anti-sense oligo.

35

The foregoing examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

## CLAIMS

1. An agent, comprising an oligonucleotide which is anti-sense to at least two mRNAs selected from the group consisting of target genes, coding and non-coding regions of RNAs corresponding to target genes, the genes' initiation codons, genomic flanking regions, intron-exon borders, the 5'-end, the 3'-end and the juxta-section between coding and non-coding regions and all segments of RNAs encoding proteins associated with one or more disease(s) or condition(s) or mixtures thereof.

2. The agent of claim 1, wherein one mRNA encodes a protein selected from the group consisting of transcription factors, stimulating and activating factors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensins, growth factors, vasoactive peptides and receptors, and binding proteins, or corresponds to an oncogene.

3. The agent of claim 2, wherein the encoded receptors and peptide transmitters selected from the group consisting of sympathomimetic receptors, parasympathetic receptors, GABA receptors, adenosine receptors, bradykinin receptors, insulin receptors, glucagon receptors, prostaglandin receptors, thyroid receptors, androgen receptors, anabolic receptors, estrogen receptors, progesterone receptors, receptors associated with the coagulation cascade, adenylyltransferase receptors, adenylyltransferase peptide transmitters, and histamine receptors (HisR).

4. The agent of claim 2, wherein the encoded sympathomimetic receptors and parasympathomimetic receptors are selected from the group consisting of acetylcholinesterase receptors (AChE), acetylcholine receptors (AChR), atropine receptors, muscarinic receptors, epinephrine receptors (EpiR), dopamine receptors (DOPAR), tachykinin receptors, and norepinephrine receptors (NEpiR).

5. The agent of claim 2, wherein the encoded enzymes are selected from the group consisting of synthetases, kinases, oxidases, phosphatases, reductases, polysaccharide, triglyceride, and protein hydrolases, esterases, elastases, and , polysaccharide, triglyceride, lipid, and protein synthetases.

6. The agent of claim 5, wherein the encoded enzymes are selected from the group consisting of tryptase, inducible nitric oxide synthase, cyclooxygenase (Cox), MAP kinase, eosinophil peroxidase,  $\beta$ 2-adrenergic receptor kinase, leukotriene c-4 synthase, 5-lipoxygenase, phosphodiesterase IV, metalloproteinase, CSBP/p38 MAP kinase, neutrophil elastase, phospholipase A2, cyclooxygenase 2 (Cox-2), fucosyl transferase, I $\kappa$ B kinase 1 and 2, chymase, protein kinase C, thymidylate synthetase, tryptase, dihydrofolate reductase,

tryptase, thymidine kinase, deoxycytidine kinase, and ribonucleotide reductase.

7. The agent of claim 2, wherein the encoded factor is selected from the group consisting of NfκB transcription factor, granulocyte macrophage colony stimulating factor (GM-CSF), AP-1 transcription factor, monocyte activating factor, neutrophil chemotactic factor, granulocyte colony-stimulating-factor (G-CSF), NFAT transcription factors, platelet activating factor, tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ), and basic fibroblast growth factor (BFGF).

8. The agent of claim 2, wherein the encoded adhesion molecule is selected from the group consisting of the intracellular adhesion molecules 1 (ICAM-1), 2 (ICAM-2) and 3 (ICAM-3), vascular cellular adhesion molecule (VCAM), endothelial leukocyte adhesion molecule-1 (ELAM-1), GATA transcription factor, neutrophil adherence receptor, mad CAM-1,

9. The agent of claim 2, wherein the encoded cytokines, lymphokines and chemokines are selected from the group consisting of the interleukin-1 (IL-1), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-11 (IL-11), CCR-5 CC chemokine, and Rantes.

10. The agent of claim 2, wherein the encoded receptor is selected from the group consisting of the adenosine A<sub>1</sub> receptor, adenosine A<sub>2B</sub> receptor, adenosine A<sub>3</sub> receptor, endothelin receptor A, endothelin receptor B, IgE high affinity receptor, muscarinic acetylcholine receptors, substance P receptor, histamine receptor, CCR-1 CC chemokine receptor, substance P, NK-1, and NK-3 receptors, CCR-2 CC chemokine receptor, CCR-3 CC chemokine receptor (Eotaxin Receptor), interleukin-1 $\beta$  receptor (IL-1 $\beta$ R), interleukin-1 receptor (IL-1R), interleukin-1 $\beta$  receptor (IL-1 $\beta$ R), interleukin-3 receptor (IL-3R), CCR-4 CC chemokine receptor, cysteinyl leukotriene receptors, prostanoid receptors, interleukin-1 receptor (IL-1R), interleukin-4 receptor (IL-4R), interleukin-5 receptor (IL-5R), interleukin-8 receptor (IL-8R), interleukin-9 receptor (IL-9R), interleukin-11 receptor (IL-11R), bradykinin B2 receptor, sympathomimetic receptors, parasympathomimetic receptors, GABA receptors, adenosine receptors, bradykinin receptors, insulin receptors, glucagon receptors, prostaglandin receptors, thyroid receptors, androgen receptors, anabolic receptors, estrogen receptors, progesterone receptors, receptors associated with the coagulation cascade, adenohipophyseal receptors, and histamine receptors (HisR).

11. The agent of claim 2, wherein the encoded protein is selected from the group consisting of the eotaxin, major basic protein, preproendothelin, eosinophil cationic protein, P-selectin, STAT 4, STAT 6, c-mas, NF-Interleukin-6 (NF-IL-6), MIP-1 $\alpha$ , MCP-2, MCP-3, MCP-4, cyclophilins, PDG2, cyclosporin A-binding protein, FK5-binding protein, fibronectin, LFA-1 (CD11a/CD18), PECAM-1, C3bi, PSGL-1, CD-34, substance P, p150,95, Mac-1 (CD11b/CD18), VLA-4, CD-18/CD11a, CD11b/CD18, C5a, CCR1, CCR2, CCR4, CCR5, and LTB-4.

12. The agent of claim 2, wherein the encoded defensin is selected from the group consisting of the defensin 1, defensin 2, and defensin 3.

13. The agent of claim 2, wherein the encoded selectin is selected from the group consisting of  $\alpha 4\beta 1$  selectin,  $\alpha 4\beta 7$  selectin, LFA-1 selectin, E-selectin, P-selectin, and L-selectin.

14. The agent of claim 2, wherein the mRNA corresponds to an oncogene selected from the group consisting of ras, src, myc, and bcl-2.

15. The agent of claim 1, wherein at least one mononucleotide linking phosphodiester residue of the anti-sense oligonucleotide(s) is substituted by a residue selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methylimino), methyleneoxy (methylimino), 2'-O-methyl, phosphoramidate residues, and combinations thereof.

16. The agent of claim 15, wherein all phosphodiester residues are substituted.

17. The agent of claim 1, wherein the anti-sense oligonucleotide comprises about 7 to 60 mononucleotides.

18. The agent of claim 1, wherein the oligo consists of up to and including about 15% A.

19. The agent of claim 1, wherein the oligo is adenosine-free.

20. The agent of claim 1, wherein the anti-sense oligo is selected from the group consisting of oligos comprising SEQ ID NOS.: \_\_ through \_\_, SEQ. ID NO:s\_\_ to \_\_ and SEQ. ID NOS: \_\_ to \_\_ (FRAGMENTS NOS: \_\_ to \_\_).

21. The agent of claim 1, wherein at least one A is substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A<sub>1</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A<sub>2a</sub> receptor.

22. The agent of claim 21, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH<sub>2</sub>, primary, secondary and tertiary amine, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, cycloalkyl, heterocycloalkyl and heteroaryl.

23. The agent of claim 22, wherein the pyrimidines and purines are substituted at positions 1, 2, 3, 4, 7 and 8.

24. The agent of claim 23, wherein the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline  
5 piperazine, bamifylline, enprofylline and xantine having the chemical formula

wherein  $R^1$  and  $R^2$  are independently H, alkyl, alkenyl or alkynyl and  $R^3$  is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl,  $NH_2$ -alkylamino-ketoxyalkyloxy-aryl and mono and dialkylaminoalkyl-N-alkylamino- $SO_2$  aryl.

10 25. The agent of claim 24, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.

15 26. The agent of claim 1, where a methylated cytosine ( $mC$ ) is substituted for at least one CpG dinucleotide if present in the oligo(s).

27. The agent of claim 1, wherein the anti-sense oligonucleotide is operatively linked to a cell internalized or up-taken agent or to a eukaryotic or prokaryotic vector.

20 28. The agent of claim 27, wherein the cell internalized or up taken agent is selected from the group consisting of transferrin, asialoglycoprotein, and streptavidin.

29. A composition, comprising the agent of claim 1 and a pharmaceutically or veterinarily acceptable carrier.

30. The composition of claim 29, wherein the carrier is selected from the group consisting of gaseous, liquid and solid carriers.

25 31. The composition of claim 29, further comprising an agent selected from the group consisting of other therapeutic compounds, surfactants, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants, RNA inactivating agents, antioxidants, flavoring agents, propellants and preservatives.

30 32. The composition of claim 29, wherein the anti-sense oligonucleotide is present in an amount of about 0.01 to about 99.99 w/w of the composition.

33. The composition of claim 32, comprising the nucleic acid, a surfactant and a carrier.

34. The composition of claim 33, wherein the surfactant is selected from the

group consisting of surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant protein and active fragments thereof, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholin, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, artificial lamellar bodies vehicles for surfactant components, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100, ALEC, Exosurf, Survant and Atovaquone.

35. A formulation, comprising the composition of claim 26, wherein the carrier comprises a hydrophobic carrier.

36. The formulation of claim 35, wherein the carrier comprises lipid particles or vesicles.

37. The formulation of claim 36, wherein the vesicles comprise liposomes and the particles comprise micro crystals.

38. The formulation of claim 35, wherein the lipid vesicles comprise N-(1-[2, 3-dioleoxyl] propyl) -N,N,N- trimethyl- ammonium methylsulfate.

39. The formulation of claim 34, comprising a respirable formulation.

40. The formulation of claim 34, comprising an aerosol.

41. The formulation of claim 34, in single or multiple unit form.

42. The formulation of claim 34, in bulk.

43. A capsule or cartridge, comprising the composition of claim 26.

44. A kit, comprising a delivery device, in a separate container, the composition of claim 26 and instructions for its use.

45. The kit of claim 44, wherein the delivery device comprises a nebulizer which delivers single metered doses of the formulation.

46. The kit of claim 44, wherein the nebulizer comprises an insufflator, and the composition is provided in a piercable or openable capsule or cartridge.

47. The kit of claim 44, wherein the delivery device comprises a pressurized inhaler, and the composition comprises a suspension or solution of the agent.

48. The kit of claim 44, further comprising in a separate container an agent selected from the group consisting of other therapeutic compounds, surfactants, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants, cell internalized or up taken agents, RNA inactivating agents, antioxidants, flavoring agents,



propellants and preservatives.

49. The kit of claim 48, wherein the surfactant is selected from the group consisting of surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant protein and active fragments thereof, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholin, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, artificial lamellar bodies vehicles for surfactant components, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100, ALEC, Exosurf, Survant and Atovaquone.

50. The kit of claim 44, wherein the composition is provided in a capsule or cartridge.

51. A cell, comprising the agent of claim 1.

52. A method of treating a disease or condition associated with the mRNA corresponding to at least one target gene(s), genomic flanking regions, or proteins, comprising administering to a subject afflicted with the disease or condition the agent of claim 1, comprising an amount of the anti-sense oligonucleotide effective to reduce the production or availability, or to increase the degradation by the subject of at least one of the target mRNA.

53. The method claim 52, wherein the agent is administered in an amount effective to reduce the production or availability, or to increase the degradation of at least two of the target mRNAs.

54. The method of claim 52, wherein the agent is administered directly to the lung (s) of the subject.

55. The method of claim 54, wherein the agent is administered as a respirable aerosol.

56. The method of claim 52, wherein the disease or condition is a lung disease or condition, and at least one of the target mRNA encodes a protein selected from the group consisting of the adenosine A<sub>1</sub> receptor, adenosine A<sub>2</sub>B receptor, adenosine A<sub>3</sub> receptor, and bradykinin B2 receptor.

57. The method of claim 56, wherein the disease or condition is associated with obstruction of the subject's airways.

58. The method of claim 57, wherein the disease or condition is associated with asthma.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/19419

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/70, 48/00; C07H 21/00, 21/04; C12N 5/10

US CL : 435/325, 375; 514/44; 536/24.5

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/325, 375; 514/44; 536/24.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	<del>WO 93/23551-A</del> (ZENECA LIMITED) 25 November 1993, see abstract, page 4, line 19, to page 5, line 13.	1, 2, 5, 17, 27, 51-53 ----- 3, 4, 6-16, 18-26, 28-50, 54-58
Y,P	WO 98/23294 A1 (EAST CAROLINA UNIVERSITY) 04 June 1998, see page 3, line 23, to page 29, line 24, especially pages 3-4, bridging sentence.	1-58

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/19419

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 20, 24, and 25  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/19419

### B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN (BIOSIS, CAPLUS, INPADOC, LIFESCI, MEDLINE, WPIDS)

Search Terms: antisense, multitarget, multi, multiple, two, targets, asthma, transcripts, receptor, synthetase, synthase, phosphatase, csterase, Nyce, Jonathan.

### BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

Claim 20 could not be search because the SEQ. ID. NOS. are missing from the claim and because a copy of the sequence listing in computer readable format (CRF) was not provided (see PCT/RO/101, Box No. VIII, item no. 8).  
Claim 24 and dependent claim 25 could not be examined because claim 24 is missing the chemical formula recited in the claim.